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ENDOCRINOLOGY

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THE QUANTITATIVE RELATIONSHIP BETWEEN STILBESTROL RESPONSE AND DIETARY "FOLIC ACID" IN THE CHICK

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"FOLIC ACID," one of the more recently identified factors of the B-complex, has been shown to be essential for normal growth and hemopoiesis in the chick (Stokstad, 1938 & 1940; Hogan, 1940). We have previously reported that the oviducts of chicks which are deficient in this important dietary factor exhibit only a slight weight increase in response to stilbestrol as compared to the marked hypertrophy of the oviduct observed in control animal receiving "folic acid" (Hertz, 1944).

We wish to report further studies indicating a direct quantitative relationship between the degree of oviduct response to stilbestrol and the dietary level of "folic acid." In addition, we have observed that the oviduct response in chicks fed a commercial stock diet is substantially greater than that observed in chicks maintained on a purified diet containing adequate amounts of the known vitamins in pure form. We have also tested the effect of feeding increasing levels of several concentrates from liver, spinach, and yeast upon the oviduct response to stilbestrol in chicks fed a purified diet. Our earlier observation that the pantothenic acid deficient chick shows an adequate oviduct response has been shown to apply also to riboflavin and pyridoxine deficient chicks (Hertz, 1944).

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MATERIALS AND METHODS

New Hampshire Red chicks were maintained from the third day of life on either a commercial starting mash[2] or on a purified diet containing the following ingredients in each 100 grams: Vitamin-free casein, 25 gms.; gelatin, 10 gms.; l-cystine 0.3 gm., choline chloride 0.2 gm.; corn-starch, 52.4 gm.; cellulose, 3 gm.; Crisco, 4 gm.; salts,[3] 5 gm.; manganous sulphate, 0.1 gm.; alpha-tochopherol, 25 mgm.; 1800 U.S.P. units Vitamin "A" and 180 units Vitamin "D." Each chick on the purified diet received daily 0.05 cc. of an aqueous mixture containing: 75γ d-calcium pantothenate, 60γ riboflavin; 125γ nicotinic acid, 2.5 mgm.: i-inositol, 50γ thiamine, 0.75 mgm.: para-aminobenzoic acid, 50γ pyridoxine hydrochloride, 0.5γ of 2-methyl-1, 4-naphthoquinone, 1.5γ biotin. In order to test the adequacy of these usual daily allowances, one series of nine animals was given ten times the usual dose of this mixture (i.e. 0.5 cc.) plus an additional 50 mgm. of choline daily and each four days a mixture containing 1 mgm., alpha-tochopherol, 1000 U.S.P. units of vitamin "A" and 100 units of vitamin "D." All supplements were administered by pipette daily.

The chicks were maintained in electric-brooders at 90 F. Water and food were supplied ad libitum and artificial illumination was maintained for 12 hours daily. All animals were autopsied at 21 days of age.

The estrogen treated animals were given 0.5 mgm. stilbestrol in 0.1 cc. corn oil subcutaneously on each of the six days preceding autopsy and were sacrificed 24 hours after the last injection. The oviducts were dissected and weighed immediately to the nearest 5 mgm.

The following materials[4] were used as sources of "folic acid" and were tested for their effect upon the oviduct response at the levels indicated in Table II.

Crystalline L. Casei Factor: this is the substance isolated by Hutchings, Stokstad, Bohonos and Slobodkin (1944). The crystalline material was administered in fresh aqueous solution.

Spinach Concentrate: prepared from spinach according to the method of Mitchell *et al.* (1941). The degree of concentration was such that 2 mgms. of this material per day was sufficient to protect chicks from anemia and to maintain growth.

Yeast Concentrate "A": a crude preparation representing a six-fold concentration of the chick anti-anemia activity of whole dried yeast.

Yeast Concentrate "B": a more purified preparation representing a 160-fold concentration of the chick anti-anemia activity of whole dried yeast.

Liver Fraction "B": an 80% alcohol insoluble residue derived from the 60% alcohol precipitate from a hot water extract of whole fresh liver; 1 gm. equals 25 gms. fresh liver.

Liver Eluate I & II: the ammoniacal alcohol eluate of a norite adsorbate prepared from a hot water extract of whole fresh liver; 100 mgms., of Eluate I equals 800 gms. of fresh liver and 100 mgms. of Eluate II equals 900 gms. of fresh liver.

[2] Purina chick starting mash.

[3] Salt mixture made according to Spicer, *et al.* Public Health Reports 57, 2, 1942.

[4] We wish to express our thanks to Dr. E. L. R. Stokstad, Lederle Laboratories, for the crystalline l. casei factor; to Drs. H. Petering and J. Waddell, DuPont Organic Chemicals Division, for the yeast concentrates, and to Dr. A. L. Caldwell, Lilly Laboratories, for the spinach concentrate.

TABLE I. OVIDUCT AND BODY WEIGHTS OF STILBESTROL TREATED CHICKS ON PURIFIED DIET

Supplement[1]	No. of chicks	Daily dose, mgms.	Oviduct (Mgms.)		Body weight (Mgms.)	
			Mean	Range	Mean	Range
Crystalline	5	0.010	241	135– 325	134	101–157
L. Casei	5	0.020	637	600– 695	143	130–156
Factor	5	0.050	777	730– 885	152	119–175
Spinach	9	2.0	256	180– 400	128	80–172
Concentrate	9	20.0	682	350– 870	123	75–190
	5	60.0	831	650– 950	112	90–130
Yeast	8	50.0	514	385– 640	99	74–125
Concentrate	9	150.0	589	430– 700	168	126–180
A	5	400.0	757	620– 945	127	108–151
Yeast	5	5.0	716	610– 980	100	86–113
Concentrate	5	15.0	748	540– 870	117	92–145
B	5	30.0	815	670– 900	103	70–122
Liver	5	5.0	403	245– 595	116	79–134
Eluate	5	10.0	641	425– 850	135	119–136
I	5	20.0	752	475–1010	137	111–164
	5	60.0	943	725–1150	150	124–173
	5	100.0	1100	730–1275	169	127–213
Liver	6	50.0	174	110– 280	115	68–144
Fraction	10	100.0	376	240– 505	130	88–172
B	4	250.0	527	450– 640	142	126–165
	10	500.0	926	695–1295	136	107–180
	9	700.0	1049	750–1320	142	117–165
Liver	10	20.0	609	300–1015	161	120–218
Eluate	9[2]	20.0	774	325–1040	164	124–221
II	9[3]	20.6	645	330–1220	103	77–143
	7[4]	20.0	550	335–1070	75	58– 98
	8	0	66	35– 85	63	47– 82
	8	0	63	40– 75	79	70– 87
None	5	0	70	60– 120	98	65–139
	5	0	85	55– 105	84	54–112
	9	0	79	55– 120	74	53– 82
	9	0	101	65– 215	85	66–107

[1] See text for description of supplements.
[2] (A) Ten-fold increase of daily allowance of known vitamins.
[3] (B) No pyridoxine added.
[4] (C) No riboflavin added.

RESULTS AND DISCUSSION

The data from 10 representative experimental series of chicks fed the stock diet are presented in Table II. The mean oviduct weight in 9 untreated birds was 24 mgms. In the stilbestrol treated series the mean oviduct weights ranged from 1090 to 1295 mgms. The ingestion of such a natural diet therefore allows for a 40 to 50-fold increase in oviduct weight in response to the oestrogenic hormone during the seven-day test period.

In stilbestrol treated chicks maintained on a purified diet without supplementation with "folic acid" the mean oviduct weights varied

from 66 mgm., to 101 mgm. in six experimental series (Table I). This striking impairment in response was found to be corrected in increasing degree as the daily dose of crystalline "folic acid" (l. casei factor) was increased. Thus, the three series of five chicks each receiving 10γ, 20γ, and 50γ, of crystalline "folic acid" daily show respective mean oviduct weights of 241, 637, and 777 mgms. Increments in response were observed with increasing levels of the "folic acid" concentrates from yeast, spinach, and liver (Table II). It is therefore apparent that within a certain range the degree of oestrogenic response varies quantitatively with the level of "folic acid" intake.

It should be emphasized that the responses obtained on the highest

TABLE II. OVIDUCT AND BODY WEIGHTS OF STILBESTROL TREATED CHICKS ON STOCK DIET

No. of chicks	Oviduct (Mgms.)		Body weight (Gms.)	
	Mean	Range	Mean	Range
7	1136	895–1300	167	149–191
5	1090	740–1200	125	88–141
5	1162	945–1340	157	120–202
8	1258	1000–1625	170	131–233
10	1228	890–1490	144	111–190
6	1161	945–1340	157	120–202
10	1198	930–1550	141	108–161
10	1136	915–1435	132	102–180
6	1161	945–1340	158	120–202
8	1295	820–1740	175	146–198
9[1]	1114	865–1380	138	102–188
9[2]	24	20– 30	175	156–225

[1] Given 500 mgm. Liver Fraction "B" daily.
[2] No stilbestrol.

dose of crystalline "folic acid" are significantly lower than those seen in the chicks receiving the stock diet. The daily requirement of "folic acid" for growth and hemopoiesis has been estimated to be between 4 and 10 gamma (Campbell, 1944; Stokstad, 1944). We have given up to 50γ daily without producing an oviduct response comparable to that consistently seen in chicks on the stock diet. Moreover, in the birds supplemented with the spinach concentrate, although the lowest dose (2 mgm.) yielded oviduct weights comparable to those obtained with 10γ of crystalline l. casei factor, a thirty-fold increase in dosage did not result in responses equal to those secured on the stock diet. A similar failure of progressive increase in response is observed in the animals supplemented with the two yeast concentrates. However, supplementation with concentrates from liver in increasing doses resulted in a proportional increase in oviduct response up to a level comparable to that obtained on the stock diet.

This difference between the effect of liver concentrates and concentrates from spinach and yeast suggests either that liver provides a factor other than "folic acid" or that the biological activity of liver

"folic acid" differs from that derived from plant sources. Solution of this problem must await further study of the comparative effects obtainable with crystalline material from each source.

In order to determine whether the stock diet afforded maximal oviduct responses, a series of 9 chicks maintained on the stock diet was supplemented with liver concentrate "B" (Table II). This resulted in no increase of oviduct weight or body weight, indicating that the stock diet was adequate for optimal effects.

It is at present not possible to evaluate the relationship between the potency of a "folic acid" preparation as tested by the various microbiological methods and its biological activity in test animals (Hutchings, 1944). We have accordingly avoided any use of the relative microbiological activity of our preparations as a basis for determining their comparative potencies. We have rather restricted our consideration to the biological effects in question, namely oviduct weight and body weight in the chick.

In evaluating the final body weights of our experimental animals it should be kept in mind that only stilbestrol treated pullets have been used. The growth-inhibiting effect of oestrogens has been described by Zondek for both the chick and the rat (Zondek, 1941). It should also be appreciated that the supplements employed may not provide adequate amounts of additional nutritional factors required by the chick (Briggs, 1943; Hill, 1944). That the identified vitamins are present in sufficient amount is shown by the absence of significant effect on body weight and oviduct weight of increasing ten-fold the daily allowance of each factor as described above.

The quantitative relationship between the degree of oviduct hypertrophy and the level of "folic acid" administered suggests that "folic acid" may play a specific role in the physiology of reproduction. Cravens, *et al.*, have previously reported the efficacy of a norite eluate from liver in improving the hatchability of eggs which had been laid by hens eating a deficient diet (Cravens, 1942).

The failure of pantothenic, riboflavin, and pyridoxine deficiencies to materially affect the oviduct response despite the accompanying arrest of general body growth further suggests some specific relationship between oestrogen metabolism and "folic acid." Several clinical and experimental reports have already indicated a similar metabolic relationship between oestrogens and other members of the B-complex. (Biskind, 1944; Segaloff, 1944; Singher, 1944; Shipley, 1944).

It should also be appreciated that the forty-fold hypertrophy of the oviduct in response to stilbestrol within seven days represents an acute demand for the rapid formation of new tissues. The direct quantitative relationship between the degree of hypertrophy and "folic acid" intake therefore suggests that "folic acid" may be critically required in new tissue formation. Moreover, this type of hormonally conditioned tissue-growth can be employed as a test-object

for the demonstration of otherwise obscure quantitative and qualitative nutritional requirements.

SUMMARY

Chicks maintained on a stock diet show a forty-fold hypertrophy of the oviduct following stilbestrol administration, whereas "folic acid" deficient chicks show only a four-fold increase in oviduct weight following identical treatment. In "folic acid" supplemented chicks, the degree of oviduct weight-increase varies directly with the level of "folic acid" ingested, but doses of "folic acid" considerably in excess of that required for growth and hemopoiesis fail to restore the oviduct response to the level obtained in chicks on a stock diet. A ten-fold increase in the usual daily allowance of the identified fat-soluble and water-soluble vitamins does not significantly affect either body weight or oviduct weight. Concentrates containing "folic acid" from yeast and spinach when given in increasing doses similarly fail to completely replace the stock diet. However, certain liver fractions effect increases in oviduct weight up to the level obtained on a stock diet. Supplementation of the stock diet with a liver concentrate affords no further increase.

Riboflavin and pyridoxine deficient chicks exhibit optimal oviduct responses, indicating that the failure of oestrogen response in "folic acid" deficient chicks is not simply a corollary of arrested body growth and general debility.

The suggested rôle of "folic acid" in the physiology of reproduction and in new tissue formation is discussed. We have also discussed the principle of utilizing a hormonally induced tissue-hypertrophy as an experimental means for demonstrating otherwise inapparent quantitative and qualitative nutritional requirements.

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A FURTHER STUDY OF THE EFFECT OF DIET ON ADRENAL WEIGHTS IN RATS

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In a review of adrenal cortical hypertrophy, Tepperman, Engel and Long (1943a) advanced the hypothesis that some substrate derived from the catabolism of either tissue or dietary protein is the stimulus to the hypertrophy of the adrenal cortex observed in a variety of circumstances. These investigators (1943b) observed hypertrophy of the adrenal cortices in immature male rats which were fed a high protein diet as compared to Purina Chow. Ingle, Ginther and Nezamis (1943) found only slightly heavier adrenals in older male rats fed a high protein diet as compared to a high carbohydrate diet which contained the same basal constituents. More recently, Benua and Howard (1945) reported that a high dietary intake of protein did not cause adrenal cortical hypertrophy in the male mouse.

In the present studies the feeding of a high casein diet similar to that used by Ingle, Ginther and Nezamis (1943) caused only small gains in the average weight of the adrenals but the feeding of the high casein diet "A" of Tepperman, Engel and Long (1943b) and of a similar high lactalbumin diet caused greater gains in adrenal weight.

METHODS

Male rats of the Sprague-Dawley strain were used. They were fed a diet of Purina dog chow until they reached a weight of either 63 to 65 grams (Experiments 2, 3, 4 and 5) or a weight of 190 grams (Experiment 1). In Experiments 1, 2, 3 and 5 the special diets (Table 1) were fed ad libitum. Within the first few weeks there was a tendency for the rats to eat smaller amounts of the casein diets than of the carbohydrate diets. During the first four weeks of Experiment 4, the amounts of carbohydrate diet fed to the rats were restricted to the same amounts of casein diet consumed by rats eating ad libitum. Thereafter all of the animals were permitted to eat ad libitum.

The carbohydrate diet C and the casein diet C were identical with those used by Ingle, Ginther and Nezamis (1943) except that the proportion of dried yeast and of cod liver oil was increased in each diet and the butterfat of the protein diet was replaced by an isocaloric amount of carbohydrate. The proportion of the total caloric value of casein diet C which was derived from protein remained approximately 67 per cent. The casein diet D was

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identical with the casein diet A of Tepperman, Engel and Long (1943b) and contained the same basal constituents as the carbohydrate diet D and the lactalbumin diet D. The proportion of the total caloric value of these protein diets which was derived from protein was approximately 80 per cent.

After the animals had been maintained on the special diets for periods of one to twelve weeks they were etherized and exsanguinated and the adrenals and thymus were rapidly cleaned and weighed.

TABLE 1. COMPOSITION OF SYNTHETIC DIETS

Constituent	Casein C	Carbohydrate C	Casein D	Carbohydrate D	Lactalbumin D
	gm.	gm.	gm.	gm.	gm.
Dried Yeast (Pabst)	150	150	100	100	100
Salt Mixture (Osborne & Mendel)	40	40	50	50	50
Cellu Flour (Chicago Diatetic Supply)	120	120			
Wheat Germ Oil	10	10			
Cod Liver Oil	30	30	20	20	20
Mazola Oil	10	10	50	50	50
Casein (Labco)	830	160	780	160	160
Dextrin	135	460		380	
Starch	135	500			
Sucrose				240	
Lactalbumin					620

EXPERIMENTS AND RESULTS

In Experiment 1 (Figure 1) 60 normal rats of 190 grams weight were divided into three equal groups for the feeding of casein C, carbohydrate C and Purina dog chow. Five rats from each group were killed at periods of one, two, four and eight weeks. The animals which were fed the casein diet gained weight more slowly than the other two groups but after eight weeks the difference was small. The differences in thymus weights paralleled the differences in body-weight. The differences in adrenal weights between the groups were small thereby confirming the results obtained by Ingle, Ginther and Nezamis (1943) using similar diets.

The same diets were used in Experiment 2 (Figure 2) as in Experiment 1. The animals had an initial weight of 63 to 65 grams. Ten rats in each group were killed at periods of two, four and twelve weeks. The results were not influenced by the use of younger animals as they were similar to the results of Experiment 1.

Experiment 3 was carried out to test the possibility that the absence of fiber in the diets might change the results. The diets were identical with casein C and carbohydrate C except that the cellulose was omitted from each diet. The animals had an initial weight of 63 to 65 grams. Ten rats in each group were killed at the end of two weeks. At this time the rats fed the casein diet had an average body-weight of 96 grams, an average thymus weight of 238 mgm. and an

average weight of pairs of adrenals of 20.4 mgm. The rats fed the carbohydrate diet had an average body-weight of 109 grams, an average thymus weight of 366 mgm., and an average weight of pairs of adrenals of 20.5 mgm. These data are not presented in the figures.

In Experiment 4 (Figure 3) the feeding of the special diets based

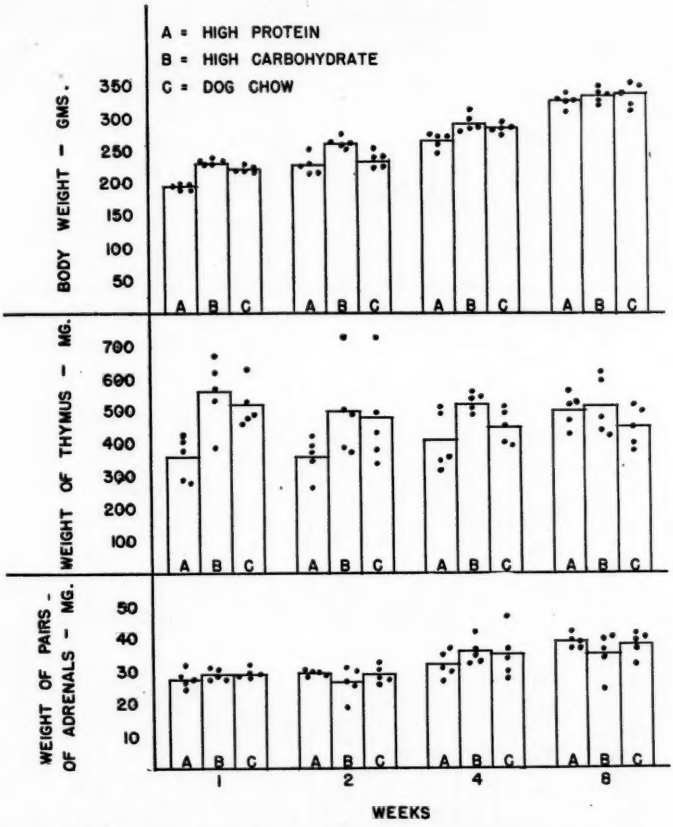

FIG. 1. Male rats having an initial body-weight of 180 grams. Diets casein C and carbohydrate C.

upon the casein A diet of Tepperman, Engel and Long (1943b) was started at a body-weight of 63 to 65 grams. The amount of carbohydrate diet was restricted for four weeks (see methods) and was thereafter fed ad libitum. Ten rats from each group were killed at periods of two, four and eight weeks. At each period the average adrenal weights were greater in the animals fed the casein diet and the size of the difference increased with the length of the period.

Experiment 5 (Figure 4) tested the effect of lactalbumin diet D on adrenal weights. The feeding of the special diets was started at a body-weight of 63 to 65 grams. The animals ate ad libitum throughout the

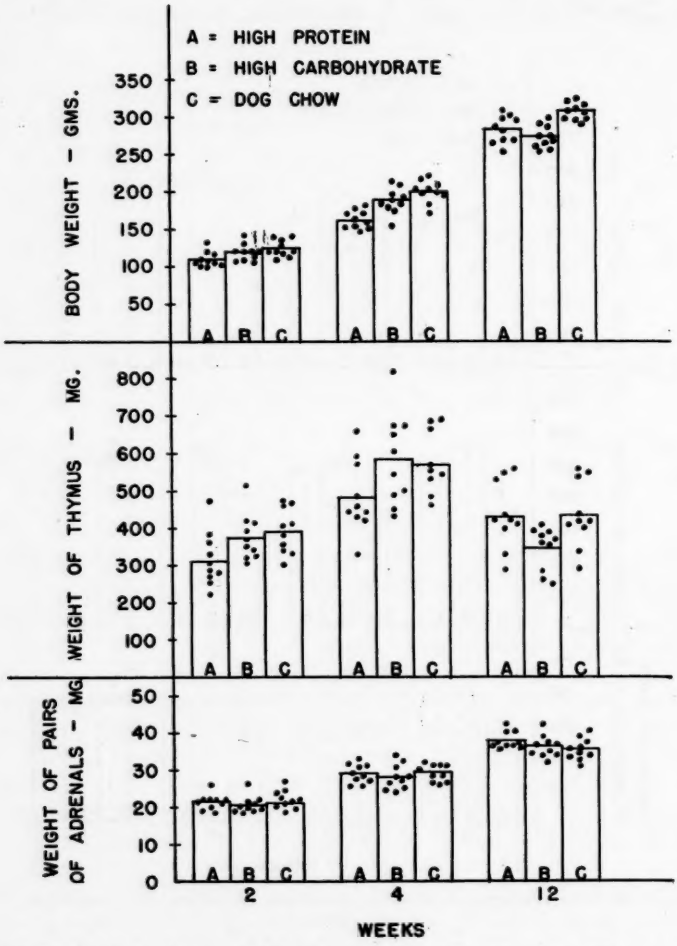

FIG. 2. Male rats having an initial body-weight of 63 to 65 grams. Diets casein C and carbohydrate C.

experiment. Ten rats from each group were killed at periods of two, four and eight weeks. The gains in body-weight were similar and at each period the average adrenal weights were greater in the animals fed the lactalbumin diet.

DISCUSSION

The results of these experiments confirm the observations of Ingle, Ginther and Nezamis (1943) and are in partial agreement with

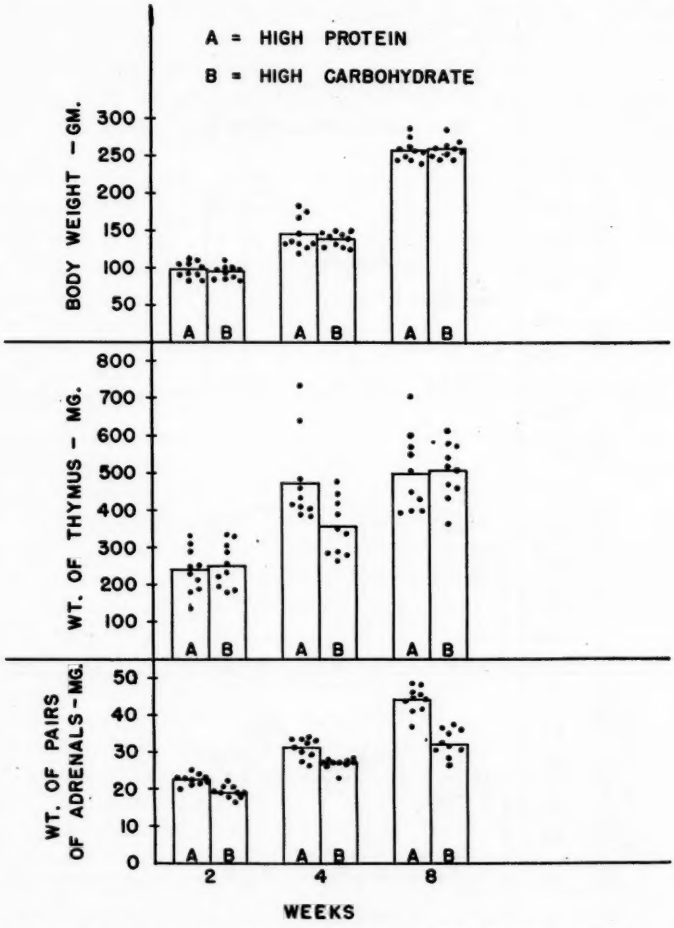

FIG. 3. Male rats having an initial body-weight of 63 to 65 grams. Diets casein D and carbohydrate D.

the data of Tepperman, Engel and Long (1943b). It is possible to induce gains in adrenal weight by feeding a high protein diet as compared to a high carbohydrate diet and the extent of hypertrophy depends upon the specific diet used. We do not have a full explanation for all of the differences in extent of hypertrophy on the same and

different diets observed in the two laboratories. Why, for example, did little or no hypertrophy occur during the feeding of casein C in this laboratory whereas Tepperman, Engel and Long (1943b) found marked hypertrophy during the feeding of their casein B which con-

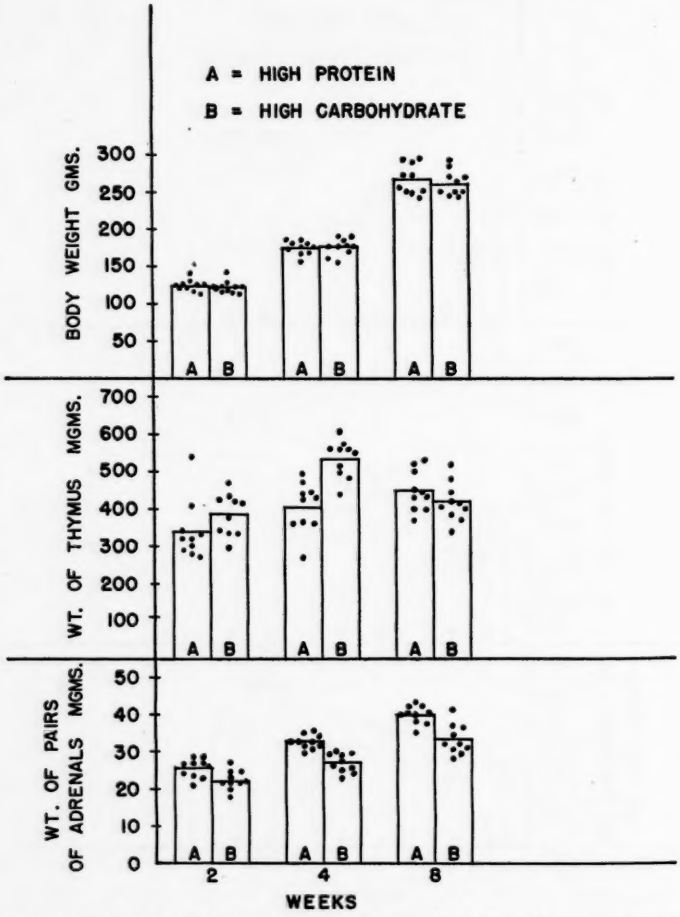

FIG. 4. Male rats having an initial body-weight of 63 to 65 grams. Diets lactalbumin D and carbohydrate D.

tained a smaller proportion of protein? Our less striking results with casein C may have been related to the subnormal consumption of this diet during the first few weeks of the experiment. On the other hand, the consumption of diet casein D was also subnormal in the early part of the experiment but the gains in adrenal weights were greater. It is

probable that the causes of the remaining discrepancies could be fully explained through further experimentation but the writer does not propose to continue studies along these lines.

The available data on the effect of diet on adrenal size can be interpreted to either support or oppose the hypothesis of Tepperman, Engel and Long (1943a) that the common denominator in all causes of adrenal cortical hypertrophy is an increase in some substrate derived from protein catabolism.

Some of the arguments against this hypothesis are as follows:

1. The hypothesis does not discriminate between the cause of adrenal cortical hypertrophy and the result of cortical hormone action. The C-11-oxygenated steroids can cause, either directly or indirectly, an increase in the catabolism of tissue proteins but such is postulated as providing a stimulus to cortical hypertrophy. Actually, the increase in tissue catabolism observed following overdosage with cortical hormones is accompanied by cortical atrophy.

2. During stress (Ingle, Ginther and Nezamis, 1943) the adrenal cortex may hypertrophy to a far greater extent than has been observed to result from the feeding of protein in either the present experiment or those of Tepperman, Engel and Long (1943b). Moreover, in some of our experiments and in the study of Benua and Howard (1945) in mice adrenal hypertrophy did not occur at all during the feeding of high protein diets.

3. From studies on the cortical hormone requirements of adrenalectomized animals it is known that it is essential for the animal to receive very large amounts of the hormone during periods of stress. If the vital need for the hormone during stress were due to its rôle in some phase of the catabolism of protein it might be assumed that it would also be vitally important for the adrenalectomized animal to receive large amounts of the hormone in order to live on a high protein diet. Ingle, Ginther and Nezamis (1943) found that adrenalectomized rats were able to live and show excellent growth on a high protein, high sodium chloride diet without supplementary treatment with cortical hormones.

4. In unpublished experiments the writer has observed definite enlargement of the adrenal glands of rats caused to die by the overfeeding of a high carbohydrate, low protein diet. It seems quite possible that a high protein diet may represent a mild, non-specific stress to the animal. There are many references in the literature to the damaging effects of high protein diets. It may be significant that the specific dynamic action of protein is greater than that of carbohydrate or fat.

None of these arguments against the hypothesis of Tepperman, Engel and Long (1943a) are inconvertible and this hypothesis which was considered conservatively by its protagonists deserves further testing.

SUMMARY

The effects of high carbohydrate and high protein diets on the weights of adrenal glands were studied in young male rats. Using a casein diet in which approximately 67 per cent of the caloric value of the diet was derived from protein it was found, in confirmation of an earlier study, that there was little or no hypertrophy as compared to the effect of a high carbohydrate diet. When high casein and high lactalbumin diets were used in which approximately 80 per cent of the caloric value of the diet was derived from protein there was a definite increase in the weights of adrenal glands above those of similar animals fed a high carbohydrate diet.

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THE COMPARATIVE EFFECTS OF ESTRADIOL, DIETHYLSTILBESTROL AND ITS MONOMETHYL ETHER ON THE RESPONSE OF THE RABBIT UTERINE ENDOMETRIUM TO PROGESTERONE,[1]

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IN AN EARLIER COMMUNICATION (Werthessen, Gargill, Berman and Greenberg, 1945) we reported the effect of estradiol, stilbestrol, and its monomethyl ether on the growth of the early rabbit blastocyst. The animals in the series had been ovariectomized and received the same dosage of progesterone (0.42 mgs.) combined with varying concentrations of the 3 estrogens.

In brief, it was found that estradiol had no effect on blastocyst growth under these conditions while stilbestrol and its monomethyl ether inhibited blastocyst growth. The ether was found to be at least 4 times more active than the parent compound.

At the same time at which the above data were obtained the uteri of the animals were preserved for later examination. The results of this examination are to be reported here. In addition, certain other experiments whose value was indicated by these results will be reported.

METHODS

The rabbits used in this work (adult females of intermediate size and strains) were ovariectomized 16 to 24 hours after copulation. Progesterone in doses of 0.07 mgs. was administered subcutaneously twice daily beginning the day after ovariectomy. With the second daily injection, $\frac{1}{3}$ the total dose of estrogen was administered intraperitoneally each day for 3 days. The animals were killed on the day following cessation of injection. The uteri were fixed immediately in Bouin's solution.

Sections were cut in such fashion that a very close approximation of a true cross section of the uterus was obtained. In order to reduce the variation and to obtain a closer approximation of the development of the endometrium at least 4 pieces of tissue were fixed and sectioned. 4 to 5 sections of each uterine sample were cut. Readings were made from at least 2 sections out of the 16 to 20 available. Choice of section was made by determining the best cross sections out of 2 separate samples from the uterus. The criteria

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[1] Aided by grant from Wallace-Tiernan Company.

of acceptability of the sections were (a) central position of lumen, (b) evenness of section and lack of folding, (c) freedom from tears, cracks, etc. in the endometrium.

The section outlines were projected onto paper and the inner lining of the myometrium was traced. The lining of the lumen and the boundary line between the glandular portion of the endometrium and the mucosal portion was also traced. The area of traced outlines of the endometrium was measured with a planimeter. The ratio of glandular to total endometrium or (G/M) has been shown to be a function of the amount of progesterone administered (Pincus & Werthessen, 1937).

We hoped to employ this type of mensuration to determine whether the administered estrogens could alter the endometrial response to our standard dose of progesterone.

It should be noted that the mouths and lumina of the glands were not considered as a portion of the uterine lumen when traced. The line denoting the edge of the endometrium is continuous from one edge of the gland across the mouth of the gland to the opposite edge. *Therefore*, this technique of assay does *not* take into consideration the extent of glandular development, but only the relative areas of endometrium which have or have not responded to the progestational stimulus.

The Astwood technique of estrogen assay was employed in one study (Astwood 38). The hormone was administered intraperitoneally in 0.2 cc. of olive oil.

The effects of the compounds on implantation inhibition as previously studied by Pincus and Kirsch (1936) was also reinvestigated. The technique consisted of injecting intraperitoneally, a pregnant rabbit on the 3rd and 4th days of its pregnancy with the estrogen under study. On the 10th day of pregnancy the animals were killed and the number of implantation sites compared with the number of corpora lutea.

RESULTS

(1) Effects of the estrogens on the G/M ratio.

The G/M ratios are presented in table 1. Calculations made upon these values provide the following:

(1) The G/M ratios for the animals receiving stilbestrol at 210 and 105 gamma dosage levels were averaged and compared with the control series. A difference of 0.16 ratio units less was found and is apparently significant. The data obtained on the animals receiving 53 gamma of stilbestrol showed an average ratio of 0.43. This too, was significantly different from the control size ($p = <.01$).[2]

(2) The animals receiving the same dosage (in gamma) of monomestrol were similarly treated. The average was found *not* to be different from the control series.

(3) The estradiol injected groups which had received the 2 highest dosages showed no significant difference from the controls or the monomestrol group.

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[2] p values calculated by use of the t test (Snedecor).

TABLE 1. DATA ON ENDOMETRIAL RESPONSE

Values for G/M obtained on the uteri of rabbits. All animals except unoperated controls and uninjected controls received 2 injections of 0.07 mg. progesterone per day for 3 days beginning day after ovariectomy. Animals killed 16 to 20 hours after last injection. Estrogens were administered intraperitoneally. ⅓ total dose with second daily injection of progesterone.

Rabbit no.	Gamma of estrogen[1]	G/M
	INJECTED CONTROLS	
4	0	.64
7	0	.52
57	0	.40
62	0	.54
69	0	.79
73	0	.63
78	0	.65
134	0	.59
127	0	.60
		average = 0.60
	UNOPERATED CONTROLS	
8	0	.61
9	0	.79
	UNINJECTED CONTROLS	
77	0	.23
71	0	.31
68	0	.35
	ESTRADIOL	
135	180	.48
137	180	.43
138	180	.57
140	252	.69
141	252	.53
143	252	.43
145	297	.53
		average = 0.52
	MONOMETHYL ETHER OF STILBESTROL	
17	105	.52
22	105	.50
14	210	.58
94	210	.54
95	210	.55
21	210	.50
		average = 0.53
	DIETHYL STILBESTROL	
91	53	.48
90	53	.61
84	53	.45
83	53	.36
92	53	.37
46	53	.26
31	53	.47
		average = 0.43
Probability this value same as control = < .01.		
93	105	.34
32	105	.59
30	105	.38
19	105	.52
80	210	.47
79	210	.34
24	210	.45
		average = 0.44
Probability this value same as control = < .01.		

[1] Total amount of estrogen administered.

These findings—namely that estradiol and the monomethyl ether had no apparent effect on the endometrium led us to re-examine the data on implantation inhibition by the natural estrogens observed by Pincus and Kirsch (1936).

They found that estradiol was an extremely potent inhibitor of implantation. 50 I.U. given in 25 unit doses intraperitoneally on the 3rd and 4th day respectively of the rabbit's pregnancy were capable of completely inhibiting implantation.

Our data—while not immediately relevant to implantation—suggested, however, the need for restudy. To determine whether our

TABLE 2

The ratio of uterine weight to body weight found in immature female rats (40 to 60 grams in weight) after the injection of estrogens intraperitoneally dissolved in 0.2 cc. of olive oil.
(Note—Uninjected ratio averages 0.46. Maximum average effect 0.72.)

Dose	No. of rats	Values	Average
0.26 gamma Stilbestrol	7	.73, .55, .52, .56, .52, .61, .60	0.58
0.26 gamma Monomethyl Ether of Stilbestrol	7	.62, .61, .65, .73, .67, .77, .62	0.67

Probability that these two groups are the same = <.05 >.01.

findings could be applied, we followed the procedure of Pincus and Kirsch in detail using estradiol benzoate and estradiol.

Estradiol benzoate did not inhibit until very high dosages were employed. If the earlier results were due to contamination, a repetition of the experiment with 200 gamma of estradiol[3] (100 gamma per day) should show at most only incomplete inhibition. We found (table 3) that estradiol could not be considered a potent inhibitor of implantation in the sense that the data of Pincus and Kirsch indicated.

Similar experiments using stilbestrol and the monomethyl ether likewise indicated that they had a low potency as inhibitors of implantation.

In light of the above, it seemed imperative to recheck the findings of estrone (table 3). A total of 200 gamma of estrone did not inhibit implantation, contrary again to the findings of Pincus and Kirsch. 150 gamma of the compound did again, as in our earlier work, inhibit blastocyst growth and endometrial differentiation (Table 3A).

A small series of animals was used to test the response of the uterus to the 2 synthetic estrogens by the 6 hour Astwood technique. Here

[3] Through the courtesy of Dr. Pincus and Dr. Mather, a small amount of very highly purified estradiol was obtained.

TABLE 3 AND 3A

Effect on blastocyst growth and implantation in pregnant animals injected with estrogens. (Normal control values are 90 to 100% implantation and blastocyst growth equivalent to 43 units.) All estrogens were injected intraperitoneally once daily on days of pregnancy noted in table. In table 3A are 2 animals demonstrating previously observed effect of estrone in inhibiting blastocyst growth supported by 0.42 milligrams of progesterone. Values given are significantly different from control level found in earlier communication.

Rabbit no.	Day of pregnancy and amount of injection in gamma	Total dose estrogen in gamma	Day of pregnancy observed	Effect (blastocyst size in units or % implantation)[1]
		Diethyl Stilbestrol		
20	(100) days 2, 3, 4	300	5	54, 51, 50, 52, 51, 47, 52, 47, 50, 55, 55
		Monomethyl Ether of Stilbestrol		
17	(100) days 2, 3, 4	300	5	38, 36, 40, 43
18	(100) days 2, 3, 4	300	5	45, 47, 49, 39, 53, 27, 15, 56,
31	(100) days 3, 4	200	10	85%
		Estradiol		
19	(80) days 2, 3, 4	240	5	29, 46, 45, 52, 52, 52, 50, 47, 35, 31, 33
25	(100) days 3, 4	200	10	0%
27	(100) days 3, 4	200	10	100%
28	(100) days 3, 4	200	10	27%
		Estradiol Benzoate		
21	(22) days 3, 4	44	10	100%
22	(50) days 3, 4	100	10	87%
23	332 on day 3 166 on day 4	498	10	75%
24	332 on day 3 166 on day 4	498	10	36%
26	332 on day 3 166 on day 4	498	10	44%
		Estrone		
29	(100) days 3, 4	200	10	90%
30	(100) days 3, 4	200	10	50%
		Table 3A		
31	(0.14 mg. progesterone 16.6 gamma Estrone) days 2, 3, 4	50	5	14, 14
32	(0.14 mg. progesterone 16.6 gamma Estrone) days 2, 3, 4	50	5	5, 5, 6, 7

[1] $\% \text{ Implantation} = \frac{\text{no. of living embryos}}{\text{no. of corpora lutea}}$.

again (table 2) the monomethyl ether is more potent than the parent substance. For the purposes of this presentation, only two comparable dosages of the several employed were selected. It is adequate to demonstrate the higher potency of the monomethyl ether. Other differences, such as the slope of the dose response curve, appear to be present and are the subject of further study.

DISCUSSION

The data presented in our earlier paper and in this communication present several new facets to the general problem of estrogenic potency as demonstrated by a particular compound.

The use of the vaginal smear as the standard of reference for potency has, to some extent, decreased the attention of observers to the other expressions of estrogenic potency a compound may exhibit. Through the use of 3 other modes of assay, we have been able to show primarily that the potency exhibited by a substance as assayed by the vaginal smear is not necessarily the same when a assay is conducted by the utilization of another test method. (Earlier communication.)

We were particularly fortunate in being able to test stilbestrol and its monomethyl ether. The only difference between these 2 compounds is the replacement of a single hydrogen by a methyl group. As a first approximation, it would be assumed that the monomethyl ether would possess all the properties of stilbestrol. Quite possibly, the methyl ether would not be excreted as rapidly as stilbestrol. From the viewpoint of duration of effect, it should, therefore, be more potent than the parent compound. Observations cited in our earlier paper supported this point of view.

Our evidence on the inhibition of blastocyst growth could be explained on this basis. But (1) the simultaneous relative non-interference with endometrial response to progesterone; (2) the greater potency of the monomethyl ether in the 6 hour Astwood assay method, indicate that the pharmacology of stilbestrol has actually been altered by the replacement of the hydroxy by a methoxy group. We feel that the exhibited properties of this compound must be considered as inherent in the compound. The differences in action between the 3 compounds studied can only be due to their chemical structure.

That there is a certain amount of miscegenation of effect in the properties of stilbestrol and the monomethyl ether is explained by the findings of Shorr and Mazer (personal communication). These observers have discovered that the excretion product of the monomethyl ether is stilbestrol. Thus, a demethylation of the ether must take place in vivo. Unless this demethylation and subsequent glucuronidation of the compound occurs at the same time, stilbestrol must be circulating, as such, when the monomethyl ether has been administered.

One effect of such a process would be a stabilization of stilbestrol concentration in the system. Such a decrease in concentration variation is to be expected on the grounds that excretion of the compound would be delayed until demethylation had occurred. It should express itself as a decrease in the variance of the observations provided the system observed were sufficiently sensitive. We observed such a decrement in variance in the blastocyst study when comparing the variance

in results found in the stilbestrol and monomethyl ether series.

Simultaneously with this reduction in variation, an increment in potency for the less rapidly degraded compound should be observed, provided the observed effect was not a short time phenomenon.

It was on the consideration of this latter point that the experiments on the rat uteri were undertaken. Since the observed increment in potency in the rabbit series could be ascribed to prolonged action of the compound, a test providing but a short time in which to function should reveal a reversal of apparent potency.

The argument that differences between the synthetics was due to prolongation of the effect of the ether was vitiated in these experiments. We found the monomethyl ether more potent as a stimulant for the imbibition of water by the uterus in a 6 hour period.

This latter finding, in our opinion, is most revealing. It leads us to the inevitable conclusion suggested above that the pharmacology of the monomethyl ether is different from that of stilbestrol. This finding also suggests that further research on the collateral properties of the estrogens is needed.

In view of our general results with estradiol, both in the ovariectomized rabbit series and in the attempt to inhibit implantation in the intact rabbit, we feel that it is not possible to ascribe a further property to this natural estrogen. This property can be considered to be at least the non-interference with the progestational phenomena when the concentration of estradiol is within physiological limits. The property of the estrogen in synergizing the effect of progesterone by sensitizing the uterus to progesterone has long been known. The finding of estradiol, estrone and estriol in the urine during the secretory phase of the human menstrual cycle has suggested an interrelation of effect.

The earlier findings (Pincus and Werthessen, 1938) and those of Pincus and Kirsch, that estrone has definite inhibitory propensities both on egg growth and implantation indicate that the "non-interference" property is not common to all the estrogens. But here again, much more study is requisite for the full elucidation of the combined effects of the estrogens and progesterone. Judging by the results we have obtained, the concentration of progesterone ought to be fully as important as the concentration of estrogen. This would appear to be the only explanation available for the findings that the synthetic estrogens did not interfere with the pregnancy in the intact animal. They were able to do so when the pregnancy was supported by a concentration of progesterone capable of developing the blastocysts to only $\frac{1}{2}$ or $\frac{3}{4}$ of the expected growth. (Earlier communication.)

The variation in amount of progesterone present probably accounts for the partial divergence of our findings from those of Pincus and Kirsch. We do not at present feel that estrogens, including estradiol, will inhibit normal gestation unless they are given in very large quantity.

But, we do feel that estrone and stilbestrol are more potent inhibitors than are estradiol and the monomethyl ether of stilbestrol as regards the endometrium. But since, as we showed in our first report, the monomethyl ether is more potent in blastocyst inhibition than stilbestrol, the ether cannot be considered a complete substitute for estradiol.

CONCLUSIONS

Estradiol has the distinct property of acting as a synergist to progesterone, not only in rendering the uterine mucosa sensitive to progesterone, but also in not interfering with the amount of response developed per unit dosage of progesterone when simultaneously administered. (Within certain limits of the ratio of estradiol to progesterone.)

Estrone and stilbestrol do not possess the property of enhancing the effects of progesterone in the uterus when administered simultaneously.

The monomethyl ether of stilbestrol possesses the properties of stilbestrol in part, but its pharmacology has been modified from that of the parent compound as follows:

(a) It is less rapidly excreted than stilbestrol. This decrement in excretion rate is reflected by (1) a greater potency than stilbestrol in inducing an inhibition in blastocyst growth, (2) less variance in demonstrating such an inhibition.

(b) The monomethyl ether differs from stilbestrol in that it fails to inhibit the endometrial response to progesterone stimulation.

(c) The potency of the monomethyl ether in stimulating the uterus in a short time assay (6 hours) is significantly greater than that of stilbestrol.

(d) In view of the fact that the monomethyl ether is excreted as stilbestrol, it must follow that the material acts in 2 forms. One form —the monomethyl ether—has distinctly different actions from the compound—stilbestrol—into which it is converted in vivo.

ACKNOWLEDGMENTS

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ACTION OF THYROXIN ON ESTROGEN-INDUCED CHANGES IN BLOOD CHEMISTRY AND ENDOSTEAL BONE

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ESTROGENS increase greatly the calcium, phosphorus and lipid content of bird plasma; they also induce growth of the oviduct and formation of endosteal bone in both birds and mammals. The literature on this subject has been reviewed by Riddle (1942) and by Gardner and Pfeiffer (1943). Riddle and Dotti (1936, 1945) noted that in pigeons thyroidectomy does not notably affect the ability of estrogens to raise the plasma calcium. Clavert (1942) reported that the hypercalcemic and osteogenic actions of estradiol dipropionate in drakes are reduced by thyroidectomy, and that these actions are restored by injections of thyroxin. Thyroidectomy has been shown to increase the cholesterol, fatty acid and phospholipid content of drake plasma (Benoit and Bogdanovitch, 1937) and the administration of thyroxin apparently decreases the fat content of pigeon plasma (Riddle, Senum and Rauch, 1945). Fleischmann and Fried (1944, 1945) made the important observation that thyroxin, when administered simultaneously (and in equal amounts) with estradiol dipropionate in immature chicks, greatly reduces the ability of the estrogen to increase the plasma calcium, inorganic phosphorus, vitellin, phospholipid and cholesterol, but does not inhibit the growth of the oviduct. The experiments reported here were undertaken to determine (*a*) whether the results obtained with simultaneous dosage of thyroxin and estrogen in fowl can be duplicated in pigeons, (*b*) whether such treatment prevents the increase of plasma neutral fat which follows the use of estrogen alone, and (*c*) to learn whether endosteal bone can be formed under the simultaneous administration of thyroxin and estradiol benzoate.

PROCEDURE

Three groups of pigeons, two immature females and two adult males per group, were given 6 daily injections of thyroxin, estradiol benzoate or thyroxin plus estradiol benzoate. Two additional groups, three adult males per group, received estradiol benzoate or thyroxin plus estradiol benzoate for 15 days. Equal amounts by weight of the two hormones were given,

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since Fleischmann and Fried (1945) observed that only under these conditions could thyroxin neutralize the effects of estradiol dipropionate. The daily dosage for the first 6 days was 0.5 mg. after which, because of fatalities,[1] it was reduced to 0.25 mg. Thyroxin[2] (1:600 solution in 0.01 M sodium hydroxide) was injected subcutaneously and estradiol benzoate (1:600 solution in propylene glycol) was injected intramuscularly. The initial body weight of the adults was approximately 450 gm. while that of the immature birds was about 330 gm.

Samples of 3 ml. blood per pigeon were taken from each group of birds during the course of the injections at intervals not shorter than 4 days; samples of 15 ml. were taken 24 hours after the final (sixth or fifteenth) injection, and immediately thereafter data on oviducal weights and femur ossification were obtained. The method used for grading femur ossification in pigeons was described by Riddle, Rauch and Smith (1944), and the methods used in sampling and measuring the various forms of plasma, calcium, phosphorus and nitrogen were described by McDonald and Riddle (1945). Plasma "fat" was determined by the volumetric method of Allen (1938), using lipokrits requiring only 0.25 ml. samples. This method measures neutral fat, sterols, sterol esters and fat soluble pigments, but not phospholipids. Entenman, Lorenz and Chaikoff (1940), however, have shown that although estradiol benzoate increases all of the lipid constituents of fowl blood the most pronounced effect is on neutral fat.

RESULTS

Fairly definite results were obtained on the three questions which prompted this study although the number of birds tested was small. The data obtained on the effect of thyroxin on the estrogen-induced changes in plasma constituents are summarized in Table 1. The large increases in calcium, protein phosphorus (serum vitellin), total nitrogen, phospholipid and "fat" which resulted from the injection of estradiol benzoate alone were not found when thyroxin was injected simultaneously with the estrogen. The values obtained for plasma "fat," phospholipid, and total nitrogen after 6 daily injections of thyroxin plus estradiol benzoate were actually lower than at the start of the experiment and about equal to those resulting from the administration of thyroxin alone. Thyroxin probably also reduced the estrogen-induced increases in inorganic phosphorus. Although enhanced values for this plasma constituent were observed in the pigeons injected with thyroxin plus estradiol benzoate, these values were no

[1] Pigeons receiving thyroxin (whether alone or with estradiol benzoate) lost weight rapidly. Four of these birds died, two after the sixth and two after the ninth injection. All surviving birds were force-fed 15 gm. grain daily after the fifth day; after the eighth day survivors were also given 1 gm. alumina gel to reduce the thyroxin-induced increase in inorganic phosphorus. Alumina gel was earlier shown to have no effect on the estrogen-induced increases in the various plasma components (McDonald and Riddle, 1945) nor on the formation of endosteal bone (Riddle, Rauch and Smith, 1945).

[2] Thyroxin was obtained from Roche-Organon, Inc. through the courtesy of Dr. R. D. Shaner. Estradiol benzoate was contributed by the Schering Corporation through the courtesy of Dr. Erwin Schwenk.

TABLE 1. THE EFFECT OF THYROXIN AND ESTRADIOL BENZOATE ON VARIOUS CONSTITUENTS OF PIGEON PLASMA

Days treated	Plasma constituents after thyroxin treatment			Plasma constituents after estradiol benzoate plus thyroxin			Plasma constituents after estradiol benzoate		
	No. of birds	Mean and range		No. of birds	Mean and range		No. of birds	Mean and range	
		Mg. per 100 ml.			Mg. per 100 ml.			Mg. per 100 ml.	
Total calcium									
0	31*	10.5	(9.5–11.7)	18*	10.5	(9.5–11.7)	7	10.6	(10.3–11.2)
2	4	11.6	(11.4–12.0)	4	14.8	(11.5–18.2)	4	19.9	(14.7–22.8)
4				3	15.1	(12.3–16.9)	3	33.4	(28.7–41.3)
6	3	12.5	(12.3–12.7)	3	15.6	(13.7–17.2)	4	28.9	(25.1–33.0)
15				1	13.2		2	27.0	(24.4–29.6)
Ultrafiltrable calcium									
0	31*	6.0	(4.4– 8.2)	18*	6.2	(4.4– 8.2)	18*	6.2	(4.4– 8.2)
6	3	5.8	(4.6– 7.9)	3	6.4	(5.8– 7.3)	4	6.4	(6.1– 6.9)
15				1	7.0		2	5.6	(5.6– 5.6)
Total inorganic phosphorus									
0	31*	4.3	(2.0– 7.6)	18*	3.5	(2.0– 7.6)	18*	3.5	(2.0– 7.6)
2	4	5.9	(3.1– 9.7)	4	5.2	(3.3– 6.4)	4	4.9	(3.8– 7.6)
4				3	4.4	(3.1– 5.1)	3	6.2	(3.9– 8.6)
6	3	7.7	(4.3–10.4)	3	6.1	(4.6– 7.2)	4	6.6	(4.7– 7.9)
15				1	4.0		2	6.8	(5.5– 8.1)
Ultrafiltrable inorganic phosphorus									
0	31*	3.5	(1.5– 6.3)	18*	3.0	(1.5– 6.3)	18*	3.0	(1.5– 6.3)
6	3	5.8	(3.7– 7.3)	3	4.5	(4.0– 5.4)	4	3.2	(2.4– 3.8)
15				1	2.8		2	3.6	(2.8– 4.4)
Protein phosphorus									
0	31*	0.8	(0.5– 1.2)	18*	0.7	(0.5– 1.2)	7	0.8	(0.5– 1.5)
2	4	1.3	(1.2– 1.4)	4	3.8	(1.4– 6.2)	4	10.6	(7.7–12.5)
4				3	5.2	(2.5– 6.7)	3	22.9	(16.6–29.9)
6	3	0.6	(0.4– 1.0)	3	3.5	(2.5– 4.8)	4	14.7	(12.4–17.1)
15				1	4.8		2	14.1	(12.8–15.3)
Lipid phosphorus									
0	31*	20.4	(13.1–28.3)	18*	20.1	(13.1–28.3)	7	22.9	(19.4–31.1)
2	4	17.3	(15.2–20.2)	4	25.9	(19.6–34.5)	4	40.9	(29.5–46.7)
4				3	21.7	(18.1–27.7)	3	66.1	(49.7–78.8)
6	3	12.0	(9.5–14.0)	3	9.4	(8.8–10.5)	4	44.5	(31.4–51.6)
15				1	11.1		2	50.8	(46.5–55.0)
"Fat" (other than phospholipid)									
0	70*	448		70*	457		70*	457	
2	4	387	(356–416)	4	514	(400–576)	4	1120	(736–1344)
4				2	364	(312–416)	3	3228	(1908–4032)
6	3	247	(128–360)	3	224	(216–232)	4	1775	(1320–2240)
15				1	261		2	2222	(2180–2265)
Total nitrogen									
0	31*	484	(363–731)	18*	525	(363–731)	18*	525	(363– 731)
6	3	317	(241–358)	3	355	(330–381)	4	611	(515– 706)
15				1	331		2	675	(673– 676)

* Data for these "control" groups were obtained previously from comparable pigeons.

greater than those observed in the pigeons receiving only thyroxin. The increases apparently occurred (except in one bird which received alumina gel[1]) in both the ultrafiltrable and nonultrafiltrable fractions; it was earlier shown (McDonald and Riddle, 1945), however, that estrogens increase only nonultrafiltrable inorganic phosphorus.

The data of Table 2 show that thyroxin did not measurably in-

hibit the estrogen-induced formation of endosteal bone. Despite the toxic dose used, medullary bone was formed in all three tests (8–15 days) in which this response might be expected (Riddle, Rauch and Smith, 1945). Other data in Table 2 show that thyroxin did not inhibit the growth-promoting action of estrogen on the pigeon oviduct.

DISCUSSION

McDonald and Riddle (1945) have shown that all of the estrogen-induced increase in nonultrafiltrable calcium not bound as colloidal

TABLE 2. EFFECT OF THYROXIN AND ESTRADIOL BENZOATE ON FEMUR OSSIFICATION AND WEIGHT OF OVIDUCT IN NORMAL PIGEONS

Treatment	Duration	Grades of ossification					Weight of oviduct (in young females)
		0	1	2	3	4	
	Days	Number of birds in each grade					Grams
Thyroxin	5–6	2	2*				0.04
Estradiol benzoate	6	4					1.65 and 1.73
	9				1		
	15				1	1	
Estradiol benzoate plus thyroxin	5–6	4					1.80 and 3.19
	8–9			2			
	15				1		

* Grade, whether 0 or 1, uncertain.

calcium phosphate is bound to the phosphoprotein, serum vitellin; no evidence was obtained for the binding of the increased calcium by phospholipid. The data presented here are in agreement with that result. When the nonultrafiltrable-noncolloidal calcium values for the thyroxin-treated pigeons are plotted against those for protein phosphorus (Fig. 1) all of the points lie, within the range of experimental error, on the regression line previously calculated (McDonald and Riddle, 1945) from data on estrogen-treated pigeons. When such data for nonultrafiltrable-noncolloidal calcium are plotted (Fig. 2) against lipid phosphorus, however, none of the points for the thyroxin-treated pigeons fall on the line of regression calculated (McDonald and Riddle, 1945) from data on normal pigeons injected with estrogen.

Caridroit (1940) found that estrogen-induced changes in the plumage of capons are not modified by the simultaneous oral administration of thyroxin (0.5–1.0 mg. thyroxin to 10 gammas estradiol benzoate). Fleischmann and Fried (1945) showed, and this was confirmed by the present study, that thyroxin does not inhibit and possibly enhances the effect of estrogen on the bird oviduct. This study has indicated that thyroxin does not prevent the formation of endosteal bone which follows estrogen administration. It therefore seems im-

probable that thyroxin is a physiological antagonist of estrogens. Its inhibiting action on the estrogen-induced increases in plasma constituents is probably a secondary effect associated with an increased metabolism and excretion of calcium, phosphorus and nitrogen.

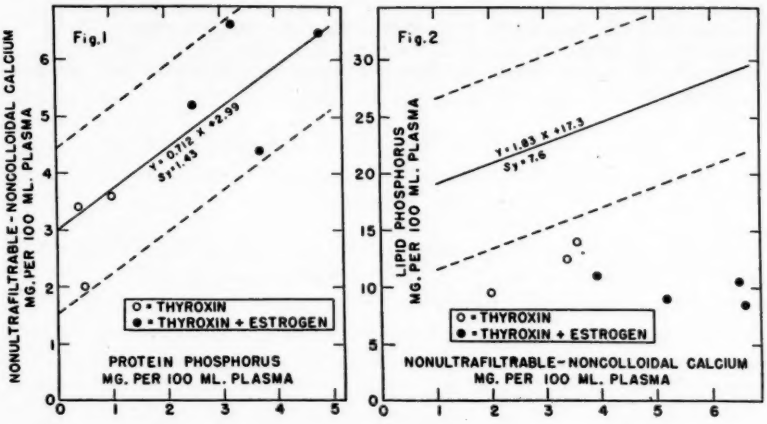
Fig.1
NONULTRAFILTRABLE - NONCOLLOIDAL CALCIUM MG. PER 100 ML. PLASMA
Y = 0.712 X + 2.99
Sy = 1.43
○ = THYROXIN
● = THYROXIN + ESTROGEN
PROTEIN PHOSPHORUS MG. PER 100 ML. PLASMA
Fig.2
LIPID PHOSPHORUS MG. PER 100 ML. PLASMA
Y = 1.83 X + 17.3
Sy = 7.6
○ = THYROXIN
● = THYROXIN + ESTROGEN
NONULTRAFILTRABLE - NONCOLLOIDAL CALCIUM MG. PER 100 ML. PLASMA

FIG. 1. Correlation between nonultrafiltrable-noncolloidal calcium and protein phosphorus. The solid line represents the regression equation previously calculated (McDonald and Riddle, 1945) from data on 104 estrogen-treated pigeons. The dotted lines indicate one standard error of estimate.

FIG. 2. Correlation between lipid phosphorus and nonultrafiltrable-noncolloidal calcium. The solid line represents the regression equation previously calculated (McDonald and Riddle, 1945) from data on 31 normal pigeons injected with estrogen. The dotted lines indicate one standard error of estimate.

SUMMARY

The ability of thyroxin to modify a number of the effects of estradiol benzoate was tested in pigeons. The two hormones were injected simultaneously and in equal quantities by weight.

Thyroxin did not measurably inhibit the action of estrogen on the formation of endosteal bone. It prevented the marked increase of plasma neutral fat which follows the use of estrogen alone.

Confirming results obtained on immature fowl by Fleischmann and Fried, thyroxin was observed to inhibit estrogen-induced increases in plasma calcium, inorganic phosphorus, protein phosphorus and lipid phosphorus; and it did not inhibit the ability of estrogen to promote growth of the oviduct.

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ANTIDIURETIC POTENCY OF THE NEUROHYPOPHYSIS OF THE CAT FOLLOWING PITUITARY STALK SECTION

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DIABETES INSIPIDUS is generally considered to be the result of a disturbance in the production or release of an antidiuretic hormone by the pars nervosa of the pituitary gland. The condition may be produced experimentally in the following ways: (1) destruction of the supraoptic nuclei of the hypothalamus by electrolytic lesions, (2) transection of the pituitary stalk, which interrupts the nerve supply to the posterior lobe, and (3) removal of the pars nervosa.

The polyuria begins immediately after this last procedure and usually continues throughout the life of the subject. The onset of the permanent polyuria after the first and second procedure is more complex. The normal course of events following interruption of the supraoptico hypophysial tract may be divided into three characteristic phases (Fisher, Ingram and Ranson, 1938):

(1) Transient phase which begins soon after the operation and lasts 1 to 7 days. There is a large increase in water exchange and the density of the urine falls sharply. This phase may last longer and merge with the permanent phase or, rarely, it may not develop.

(2) Normal interphase. This period between the transient phase and the onset of the permanent polyuria is characterized by normal water intake, urine output and urine density.

(3) Permanent phase. Its onset is marked by a definite increase in water consumption and urine excretion.

In the present investigation the antidiuretic potency of the posterior lobe of the pituitary has been determined at intervals after pituitary stalk section. If the chain of events following stalk section, as just outlined, is correlated with a loss in potency of the pars nervosa, bioassay at different time intervals following stalk section should demonstrate this relationship. If there is no correlation the explanation for the transient polyuria and the normal interphase must be attributed to some factor other than the hormonal content of the neurohypophysis.

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MATERIALS AND METHODS

Normal adult cats of average size were maintained on a daily diet of 60 grams of meat and 100 cc. of milk. Twenty-four hour measurements of water intake and of the specific gravity and volume of urine were recorded daily. The animals were paired on the basis of sex, weight and approximate age: one served as a control; in the other, under nembutal anesthesia, the pituitary stalk was cut through a subtemporal exposure. At different times after the operation a pair of cats was killed and the piutitary glands quickly removed from the skull and ground with sea sand in 0.25% acetic acid. No attempt was made to dissect the pars nervosa free from the rest of the pituitary. After thorough grinding, the resulting mixture was diluted to a known volume with 0.9% NaCl and aliquots, representing 0.00025 of the normal and 0.00025 to 0.01 of the experimental pituitary, were assayed for their potency by measuring the antidiuresis produced in dogs with diabetes insipidus (Hare, et al., 1945). The doses were intended to fall within the range of 0.5 milliunits. This was easily established for the normal pituitaries which contain, according to our assays, from 3.5–5 units of pituitrin. The correct dosage of the experimental pituitaries had to be determined in each case, and could be estimated by injecting intravenously, every 10 minutes, a dose in a graded series beginning with 0.0002 and increasing five fold steps until an antidiuresis was obtained. The assay was then performed in duplicate comparing this minimal effective dose of the degenerating pituitary to a standard of 0.00025 parts of the normal.

RESULTS

Twenty-eight cats were used in the experiment. Fifteen were normal, twelve were operated upon to sever the pituitary stalk, and one

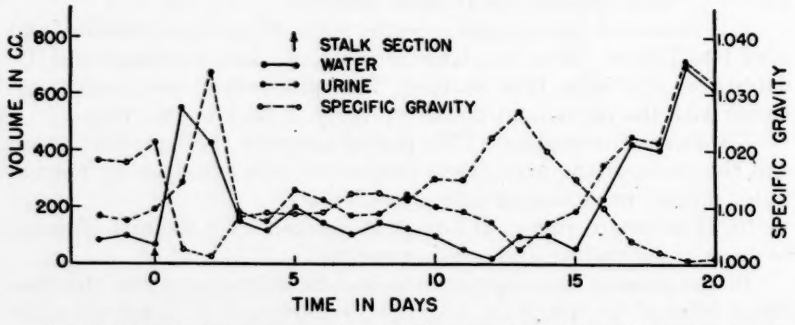

FIG. 1. Water exchange record of a cat before operation, during the transient polyuria, the normal interphase and at the beginning of the permanent phase of diabetes insipidus. The cat was killed on the twentieth post-operative day at which time the pituitary assayed 0.6% of normal.

was a cat with a diabetes insipidus of long standing produced by bilateral electrolytic lesions in the supraoptic nuclei. Its record reveals a good transient polyuria, a normal interphase and a permanent diuresis of over nine months' duration.

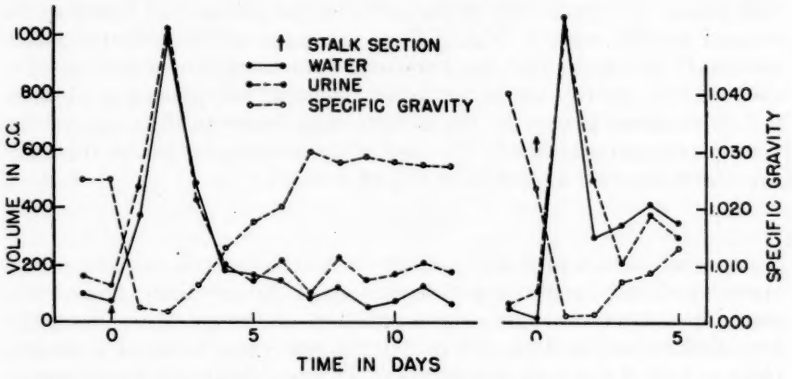

FIG. 2. Water exchange of two cats; one (left) killed late, and the other (right) early in the normal interphase. The pituitary of the first assayed 2.5% of normal; that of the second, 80%.

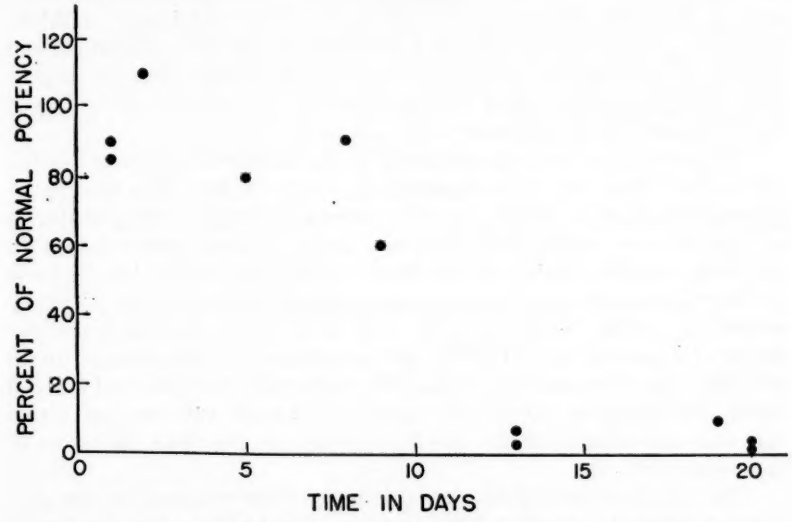

FIG. 3. A summary of eleven assays, in which the antidiuretic potency of the pituitary is plotted against the post-operative time in days.

The first few assays were run to compare the antidiuretic potencies of pituitaries from carefully paired normal cats. These agreed within 20–25% so any variation within this limit may be due to difference in cats or to inaccuracies in the assay.

The records of three selected cats are shown in the first two figures; the onset of a permanent polyuria in fig. 1, the early and late phases of the normal interphase in fig. 2. In all cases, the last day of the record indicates the day on which the cat was killed and reference to fig. 3

will permit an evaluation of the antidiuretic potency in terms of its normal paired control. Fig. 3 is a summary of these comparative assays. It is obvious that the hormonal content of the neurohypophysis is not the controlling factor in the transient polyuria or in the normal interphase; it may be the determining factor in the onset of the permanent polyuria, for in all cases of the permanent phase the antidiuretic potency was less than 5% of normal.

DISCUSSION

Several factors probably contribute to the uneven contour of the curve produced by plotting the potency of the pituitary against the time lapse after the operative separation of the pituitary from the hypothalamus. The first, which immediately comes to mind, is incomplete section of the stalk at operation. This possible error is not susceptible to check by histological study, since the removal of the pituitary at autopsy destroys the anatomical relations which need microscopic examination. It was found that the tip of the small glass suction tube, used to keep the field free of cerebrospinal fluid and blood, could be applied to the pituitary stalk just distal to the line of amputation and used as an instrument of traction to draw the tissue aside for inspection. Only animals in which this examination was wholly convincing of the complete separation were used for assay.

The second factor is the disparity in the antidiruetic content of the pituitaries from two cats superficially very similar. The finding of Simon and Kardos (1934) that the pressor content of the pituitaries of normal cats varied from 5.6–13.1 units without any relation to the body weight, which ranged from 2–4.5 Kgm. makes the hazards of direct comparison between an experimental and a normal pituitary intolerably large. While we have only four assays, in which the potency of a normal cat pituitary was compared to a standard pituitrin solution, the estimates are within the much narrower limits of 3.5–5.0 units. Furthermore direct comparisons between two normal pituitaries reveal differences that are little if any greater than the errors of the assay method.

The third uncontrollable variable is the time required for the permanent phase to develop. This in turn is probably an expression of several other factors such as the rapidity of atrophy of the pars nervosa and the hormonal requirements of the individual cat.

That the antiuretic potency is related to time rather than to gross water exchange is well brought out by a consideration of several specific cases. The pituitaries of the two cats killed the first day after stalk section, when the transient polyuria was severe, contained normal amounts of the antidiuretic hormone. This failure to conserve water in the transient phase of diabetes insipidus is obviously a failure of the antidiuretic hormone to reach the renal tubules rather than an actual loss of potency in the pars nervosa. This is further supported

by the repeated observation that injections of 1–5 milliunits of pituitrin will briefly suppress the diuresis.

Between the onset of the transient and the permanent phase the antidiuretic potency drops from 100% to less than 10%, yet the cats have a normal water exchange. For example, the cat whose record is shown on the left in fig. 2, was killed early in the thirteenth post-operative day had a water exchange almost identical with that recorded preoperatively, yet the pituitary assayed only 2.5% of normal. Thus one is led to believe that the antidiuretic potency of the pars nervosa is adequate until the permanent phase of diabetes insipidus has been reached. In other words, there appears to be a minimal requirement for antidiuretic hormone below which normal water conservation fails and polyuria and polydipsia appear. From the few results contained in this report it appears that the potency of the pars nervosa must fall below 5% of normal before the permanent phase manifests itself.

CONCLUSIONS

Following transection of the pituitary stalk in cats there is a gradual decrease in the antidiuretic potency of the pars nervosa.

There is no correlation between the water exchange and the antidiuretic potency of the pars nervosa until the permanent phase of diabetes insipidus has been reached.

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THE EFFECTS OF SEVERAL VARIETIES OF STRESS ON THE CHOLESTEROL CONTENT OF THE ADRENAL GLANDS AND OF THE SERUM OF RATS[1]

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THE CONCEPT of adrenal cortical stimulation as a consequence of non-specific stress was introduced by Selye (1937) as part of his 'alarm reaction' hypothesis. More recently, Sayers *et al.* (1944) have formulated a supplementary hypothesis relating the secretory rate of the adrenal cortex to the cholesterol content of the gland. This relationship was adduced from the finding that a single injection of purified adrenotrophic hormone into rats causes a significant decrease in the adrenal cholesterol concentration. The loss of cholesterol was interpreted as being due to an increased rate of conversion of this substance into the active cortical steroids as a consequence of the adrenal stimulation by the administered adrenotrophic hormone.

To support their hypothesis, the Yale group (Sayers *et al.*, 1944) have cited many reports in the literature which show that application of unusual stresses of many varieties cause a decrease in the 'cholesterol' concentration of the adrenal cortex. Most of such data, however, are based on histological technics which are not specific for cholesterol. In addition, these histological methods are not quantitative and therefore judgment as to whether the concentration of stainable material is appreciably altered is frequently difficult.

In the experiments reported in the present communication, rats were subjected to several varieties of stress and the cholesterol content of the adrenal glands and of the blood serum was determined by the most specific and accurately quantitative method available. The results, which at least in part support the hypothesis of Sayers *et al.* (1944), are presented below.

EXPERIMENTAL

Methods. Adult male rats of the Long-Evans strain were used throughout the experiments. The animals were fed and housed in the same manner as

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our stock colony (Levin, 1943) except for the special conditions as indicated below. At the conclusion of each experiment, the rats were anesthetized by intraperitoneal injection of sodium amytal (10 mg. per 100 gm. body weight), the thoracic cavity was opened and blood collected by direct heart puncture. The blood was allowed to clot and the clear serum was used for cholesterol determination.

The adrenal glands were rapidly removed, dissected free of adhering fat and weighed. They were then covered with 2 ml. of a mixture of acetone and ethyl alcohol (1 to 1). After addition of a small quantity of alcohol-washed sand, the adrenal tissue was finely macerated with a stirring rod. The acetone-alcohol mixture was brought to a boil on the water bath and, after being allowed to cool, the supernatent fluid was transferred to a 10 ml. volumetric flask. The tissue residue was re-extracted 4 times with 2 ml. portions of boiling acetone-alcohol. The contents of the volumetric flask were allowed to come to room temperature, diluted to the mark with the same solvent, and filtered through paper previously washed with hot alcohol and dried. Aliquots of the filtrate were used for cholesterol estimation.

Cholesterol in the adrenal glands as well as in the serum was determined by Sperry's (1938; 1942) modifications of the Schonheimer-Sperry method except that the quantities of filtrates and reagents used were increased proportionally so that the Evelyn photoelectric colorimeter could be used. Analyses were done at least in duplicate with frequent checks of the method using standard cholesterol solutions.

The stresses employed included subjection to low barometric pressure, to low temperature, and to complete starvation. The effects of administration of diethyl stilbestrol which, as indicated by several other criteria, causes adrenocortical stimulation via the anterior hypophysis were also studied. In addition, the adrenal glands and the serum of a small series of rats, treated with large doses of desoxycorticosterone acetate for another purpose, were analyzed. The detailed procedures used in each experiment are described below in the appropriate sections.

RESULTS

Low pressures. The animals subjected to low pressures were not pretreated in any way. They were permitted access to food and water at all times until the actual decompression experiment was begun. Decompression was accomplished by placing the animals in individual glass jars, each jar being connected to a vacuum pump, to a mercury manometer, and to a valve permitting regulated entrance of air. The chambers were rapidly (5 to 15 minutes were generally required) evacuated to the desired pressure which was then maintained constant within about 10 mm. Hg. by the entrance of air through the valve attached to the inlet tube. The rate of evacuation was sufficient to require a fairly rapid stream of entering air in order to maintain the desired pressure. The animals were thus subjected to low pressures but, because the air within the chambers was rapidly circulating, the carbon dioxide concentration could not increase appreciably. Pressures of 200 or 300 mm. Hg., corresponding to altitudes of 33,000 and 23,000 feet, were usually used. The lower pressure was not well tol-

erated, some animals succumbing within 15 minutes. Most of the experiments were therefore done at the higher pressure. The analytical data obtained at the two pressures were, however, similar and therefore are grouped together. The duration of the exposure periods varied from 1 to 7 hours. Return to atmospheric pressure was rapidly accomplished (5 to 10 minutes) by opening the air inlet valve. The rats, although showing definite signs of oxygen want during the exposure period, rapidly recuperated and appeared quite normal immediately after return to normal atmospheric pressure.

One group of rats was autopsied immediately after exposure. Another group, similarly exposed, was allowed an 18 hour period of recuperation at normal pressure and with access to food and water before autopsy. Animals which died while in the decompression chambers were immediately removed, autopsied, and their adrenal glands taken for cholesterol analysis.

The data, presented in Table 1, indicate that exposure of rats to low pressures for 1 to 5 hours caused a marked decrease in adrenal cholesterol concentration. The average cholesterol concentration was

TABLE 1

EFFECT OF LOW ATMOSPHERIC PRESSURE ON CHOLESTEROL OF SERUM AND ADRENALS OF RATS

Treatment	No. of rats	At autopsy		Adrenal weight		Adrenal cholesterol		Serum cholesterol
		Age	Body weight					
		days	gm.	mg.	mg./100 gm. body	per cent	total mg.	mg. per cent
None	31	106–149	284 ± 5[1]	35.2 ± 0.9	12.5 ± 0.3	3.45 ± 0.15	1.210 ± 0.019	47.2 ± 1.8
1 to 5 hours at 200–300 mm. Hg. Immediate autopsy	10	107–137	278 ± 5	32.8 ± 0.7	11.8 ± 0.3	1.80 ± 0.52	0.597 ± 0.060	44.7 ± 2.1
½ to 7 hrs. at 200–300 mm. Hg. Died during exposure	6	107–138	273 ± 13	38.1 ± 2.8	14.0 ± 0.9	1.83 ± 0.31	0.684 ± 0.099	
5 to 7 hrs. at 300 mm. Hg. Autopsy 18 hours after exposure.	8	128–149	256 ± 11	37.9 ± 1.8	14.8 ± 0.5	3.40 ± 0.27	1.273 ± 0.089	43.4 ± 1.4

[1] ± figures in this and succeeding tables are for standard deviation calculated as $\sigma = \sqrt{\frac{\Sigma(x-\bar{x})^2}{N(N-1)}}$.

almost 50 per cent below the average for the adrenals of unexposed rats. The weight of the adrenal glands was not significantly altered by the exposure and consequently it may be calculated that the total cholesterol content of the adrenal glands was approximately halved by the experimental procedure.

Animals which succumbed during exposure to low pressure likewise showed (Table 1) a loss of adrenal cholesterol, the magnitude of the decrease being almost identical with that of the animals which survived the exposure. Even one of the two animals which died after subjection to low pressure for as short a period as 15 minutes showed the marked reduction in adrenal cholesterol level.

In contrast to these results are those obtained from the rats allowed to recuperate for 18 hours at normal pressure. The adrenal

cholesterol levels of these animals were practically identical with the values obtained from untreated control rats. Evidently the adrenal cholesterol is capable of very rapid depletion but also is rapidly restored to normal levels.

The serum cholesterol concentration of rats was not altered by subjection of the animals to low pressures. The sera of the rats autopsied immediately and also 18 hours after exposure contained normal amounts of cholesterol.

Low temperature. The effect of exposure to low temperature was studied in a group of 9 rats. These were kept in a refrigerator at 0 to 5° C., with access to food and water, for periods of 16, 22, or 72 hours. Autopsies were performed immediately after exposure. As indicated by the data of Table 2, exposure to cold for 16 to 22 hours caused a decrease in the adrenal cholesterol concentration. The total cholesterol content paralleled the decrease in concentration and was about

TABLE 2

EFFECT OF VARIOUS TREATMENTS ON ADRENAL AND SERUM CHOLESTEROL LEVELS OF RATS

Treatment	No. of rats	At autopsy		Body weight loss	Adrenal weight		Adrenal cholesterol		Serum cholesterol
		Age	Body wt.		mg.	mg./100 gm. body	per cent	total mg.	mg. per cent
		days	gm.	per cent					
None	31	106–149	284 ± 5		35.2 ± 0.9	12.5 ± 0.3	3.45 ± 0.15	1.210 ± 0.019	47.2 ± 1.8
16–22 hours at 0 to 5° C. Immediate autopsy	5	105–135	281 ± 15	1.7 ± 1.3	32.1 ± 1.7	11.5 ± 0.3	2.80 ± 0.30	0.896 ± 0.104	47.1 ± 3.2
72 hours at 0 to 5° C. Immediate autopsy	4	111–139	279 ± 14	0.7 ± 0.8	35.1 ± 0.6	12.6 ± 0.4	3.79 ± 0.29	1.327 ± 0.091	50.1 ± 7.9
Completely starved for 72 hours	7	123–135	222 ± 12	16.3 ± 0.6	36.8 ± 1.3	16.8 ± 0.9	3.79 ± 0.41	1.368 ± 0.109	33.9 ± 2.4
DCA[1] 6 mg. per day for 42 days	7	133–222	233 ± 11	13.4 ± 1.7	33.6 ± 2.0	13.9 ± 0.5	3.92 ± 0.69	1.306 ± 0.256	94.0 ± 10.5

[1] DCA = desoxycorticosterone acetate. The left kidney had been removed from these rats on the day before DCA treatment was begun. They were given 1 per cent NaCl solution instead of water throughout the experimental period and for the last 24 to 48 hours prior to autopsy they were kept at a temperature of 0° C.

25 per cent below the average normal value. The statistical significance of this cholesterol loss is doubtful. The serum cholesterol concentration remained normal.

Exposure of a few rats to the low temperature for a longer period (72 hours) did not cause a further decrease in adrenal cholesterol content. In fact, after the longer exposure the adrenal cholesterol level was found to be somewhat higher than in untreated rats, indicating a complete replenishment of the losses incurred during the initial stages of the exposure.

Complete starvation. A group of 7 rats was completely starved for 72 hours. Access to water was permitted. Inspection of the data obtained from these rats (Table 2) shows that no significant alterations in gland size or cholesterol content occurred although the animals lost 16 per cent of their initial body weight. The serum cholesterol level, as might be expected, was significantly decreased.

Desoxycorticosterone administration. A small group of rats was treated with large doses (6 mg. daily in aqueous suspension) of desoxycorticosterone acetate (DCA) for 6 weeks in an attempt to induce experimental arthritis as reported by Selye *et al.* (1944). Prior to the induction of the DCA treatment, the left kidney was removed from each of the animals. Throughout the experimental period, the animals drank 1 per cent sodium chloride solution instead of water and for the last 24 to 48 hours they were kept in a refrigerator at 0° C. with access to the stock diet and to the saline drinking fluid. The data from these animals are averaged in Table 2. There was no significant

TABLE 3

EFFECT OF ADMINISTRATION OF DIETHYL STILBESTROL[1] ON CHOLESTEROL LEVELS OF SERUM AND ADRENAL GLANDS OF RATS

No. of rats	At autopsy		During experiment		Adrenal weight		Adrenal cholesterol		Serum cholesterol
	Age	Body weight		Body wt. loss					
	days	gm.	days	per cent	mg.	mg./100 gm. body	per cent	total mg.	mg. per cent
31	106–149	284 ± 5	0		35.2 ± 0.9	12.5 ± 0.3	3.45 ± 0.15	1.210 ± 0.019	47.2 ± 1.8
10	119–127	289 ± 12	1	0.5 ± 0.8	34.7 ± 1.5	12.1 ± 0.4	2.57 ± 0.22	0.898 ± 0.094	41.9 ± 2.5
4	108	247 ± 6	2	2.2 ± 0.6	36.4 ± 1.7	14.7 ± 0.7	1.04 ± 0.13	0.376 ± 0.045	21.7 ± 1.4
8	110–112	269 ± 15	3	5.3 ± 0.7	45.1 ± 2.3	17.1 ± 0.6	0.71 ± 0.04	0.322 ± 0.028	13.6 ± 1.6
11	117–143	224 ± 11	8	13.5 ± 1.2	44.7 ± 3.4	19.9 ± 0.8	0.62 ± 0.06	0.270 ± 0.027	16.3 ± 3.1
6	114–115	189 ± 10	14	22.3 ± 3.2	68.9 ± 7.2	37.1 ± 4.6	0.37 ± 0.05	0.241 ± 0.022	10.2 ± 2.7
8	121–128	190 ± 8	21	28.3 ± 1.9	54.4 ± 5.2	28.4 ± 1.6	0.36 ± 0.03	0.195 ± 0.022	14.4 ± 1.8
6	137–147	173 ± 3	34	29.1 ± 1.7	49.9 ± 4.0	28.9 ± 2.4	0.29 ± 0.04	0.137 ± 0.011	10.7 ± 1.3

[1] 0.5 mg. diethyl stilbestrol in 0.1 ml. sesame oil daily.

change in adrenal size. The averages for adrenal cholesterol concentration and content are somewhat higher than normal. The data were quite variable, the individual concentrations varying from 2.15 to 7.37 per cent. The total cholesterol content varied proportionally. Although the reason for the relatively large variation is not known, it is not unlikely that it was due, at least in part, to other aspects of the rather rigorous treatment to which these animals were subjected.

The average serum cholesterol concentration of the DCA-treated animals was 100 per cent higher than that of normal animals. The individual serum cholesterol values were quite uniformly elevated, the variability being much less than that of the adrenal values of the same rats. With the exception of rats autopsied shortly after hypophysectomy, these were the only animals in which elevated serum cholesterol levels were encountered.

Stilbestrol administration. Subcutaneous administration of diethylstilbestrol (0.5 mg. in 0.1 ml. sesame oil daily) caused a marked decrease in the cholesterol levels of the serum and of the adrenal glands (Table 3; Figure 1). It may be seen that the adrenal cholesterol stores were definitely depleted within 24 hours after a single injection of the estrogen. At this time the serum cholesterol concentration was also below the normal value, but the decrease was not yet statistically significant. Continuing treatment for an additional 24 hours caused a

further loss of adrenal cholesterol. The serum cholesterol concentration was also significantly reduced at this time. With more prolonged treatment, the cholesterol losses became progressively greater until, after two weeks of continued injections, the concentration in the adrenals fell to a value approximately one-tenth as great as that found in the glands of normal animals. After 3 or more days of treatment, the serum cholesterol level was so low that in some cases none could

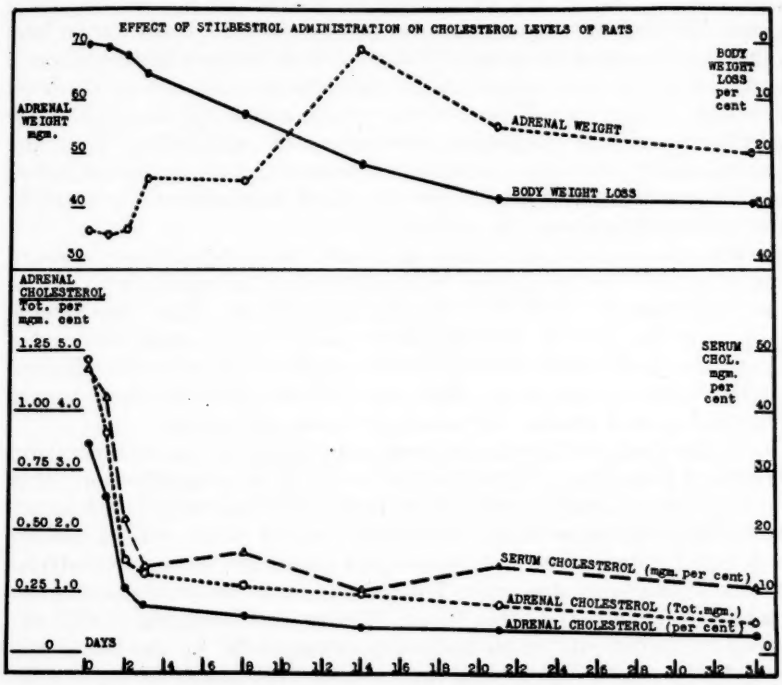

FIG. 1

be demonstrated even by the sensitive method used. At no time was there any indication of replenishment of the depleted cholesterol stores of either the serum or the adrenal glands even though treatment was continued for as long as 34 days.

As has been noted by many investigators, the weight of the adrenal glands was considerably increased by treatment with the synthetic estrogen. The greatly increased ratio of adrenal weight to body weight is, however, misleading because while the gland weight increases the animals lose a considerable proportion of their initial body weight. It should be emphasized, however, that despite the considerable adrenal hypertrophy the total amount of cholesterol in the gland de-

creased to about 11 per cent of that found in the adrenals of normal animals.

DISCUSSION

The results obtained from rats exposed to low atmospheric pressure are in agreement with the histological findings of Darrow and Sarason (1944) who reported that such treatment causes a rapid depletion of adrenocortical sudanophilic material. In our experience there was a definite loss of adrenal cholesterol after exposure for 1 hour. We did not expose rats to low pressure for sufficiently long periods to confirm the claim of Darrow and Sarason that continued exposure results in a return of the sudanophilic material to the level found in normal rats. However, our results indicate the rapidity with which the adrenal cholesterol stores may be replenished when the animals are returned to a normal environment. A recuperation period of 18 hours was sufficient for the adrenal cholesterol to be restored to the concentration found in normal rats.

It is also interesting to note that there was a marked depletion of the adrenal cholesterol of one of the two rats which died after only 15 minutes exposure to the low pressure atmosphere. That the extreme lability of the adrenal cholesterol was not the sole factor involved in the inability of certain of the animals to survive the stress is indicated by the fact that other rats, which survived the stress for much longer periods, showed similar low adrenal cholesterol values.

In the present experiments, exposure of rats to low temperature produced little change in the adrenal cholesterol concentration. This finding does not agree with that of Dosne and Dalton (1941) who reported that exposure of rats to temperatures of -3 to $-5°$ C. caused a detectable decrease in osmic acid and Sudan III stainable material within 1 hour and that after 7 days' exposure the loss became even more marked. On the other hand, Flexner and Grollman (1939) exposed rats to an environmental temperature of 10° C. and found initially an increase, but later a decrease, in the amount of osmic acid stainable material. More recently, Fry and Long (1944) found that half of the cholesterol, apparently estimated by the same method as used in the present experiments, is lost from the adrenals of rats exposed to a temperature of $-1°$ C. for 6 hours. The reason for these discrepancies is not completely apparent at this time. Unfortunately, circumstances beyond our control made it impossible to continue the present experiments. However, consideration of our results along with those of Fry and Long suggests that exposure of rats to low temperature induces a rather rapid (6 hours?) loss of adrenal cholesterol followed by a gradual restoration within the next 48 to 72 hours. It is to be hoped that information concerning this point will soon be forthcoming.

The negative results presently reported with respect to the effect of complete starvation are in good accord with previous reports (for

a review of the literature see Sayers *et al.*, 1944) which are based mainly on histological studies. However, in connection with the subsequent discussion of the effects of diethyl stilbestrol administration it is important to emphasize that complete starvation for 72 hours did not reduce the adrenal cholesterol concentration. The effect, if any, was in the opposite direction.

The treatment of rats with desoxycorticosterone has been claimed (Selye, 1940; Selye and Dosne, 1940) to cause adrenal atrophy. This findings, though not supported by the results of Wells and Kendall (1940) nor by the present data, was interpreted to mean that the administered DCA suppresses hypophyseal secretion of the adrenotrophic hormone. Such hypophyseal suppression should, according to the hypothesis of Sayers *et al.* (1944), result in a state of relative inertia of the adrenal cholesterol. The finding of normal adrenal cholesterol levels in these rats is therefore not unexpected. The elevated adrenal cholesterol levels found in a few of the animals was perhaps due to other unknown factors since the Yale group suggests that the adrenotrophic hormone is "primarily concerned in the transformation and/or removal of cholesterol from the adrenal cortex" and "is not a necessary factor in the processes concerned with the maintenance or accumulation of cholesterol in the gland."

The hypercholesteremia of the DCA treated animals may also perhaps be explained on the basis of lack of removal and utilization of the cholesterol of the serum by the resting adrenal. In accord with this idea are the similar high serum cholesterol levels found in recently hypophysectomized rats in this laboratory (Levin and Leathem, 1943) and also by the Yale group (Sayers *et al.*, 1944).

The results obtained after the administration of diethyl stilbestrol are perhaps the most striking of the present report. This estrogen acts as an adrenocorticotrophic substance as judged by several criteria. It was therefore to be expected that the administration of stilbestrol would produce an effect on the adrenal cholestrol level similar to that reported to follow the injection of pituitary adrenotrophic hormone. Since the adrenal-stimulating effect of stilbestrol is probably by way of the pituitary gland, it was also expected that its action would be somewhat slower than that of administered pituitary adrenotrophin. The early effects of stilbestrol on adrenal cholesterol level are therefore in good agreement with those obtained by direct stimulation of the adrenal cortex with adrenotrophic hormone. However, with prolonged administration of diethyl stilbestrol the adrenal cholesterol level continues to fall with no indication of return to normal values for at least 34 days, the duration of the longest experiment of the present series. This finding is difficult to reconcile with the results of Sayers *et al.* (1944) for these investigators reported that administration of adrenotrophic hormone for as short a time as 3 days yields cholesterol levels which are normal or higher than normal. The writer has no explanation to offer for this difference although it is not precluded that

stilbestrol acts upon the adrenal cholesterol in some other fashion in addition to the effect produced by eliciting adrenotrophic secretion by the hypophysis. Also, it is possible that Sayers *et al.*, by autopsying their animals 16 hours after the last of the 3-day series of injections, have missed the depletion effects since a single injection produces its maximum response in 3 to 9 hours. It should be mentioned that the Yale group postulates that continued severe stresses, overtaxing the recuperative capacity of the organism, may lead to very low adrenal cholesterol levels. Such severe stresses are said to be those eventually leading to the death of the animal. Although stilbestrol-treated animals do lose considerable body weight, the present writer has never observed deaths resulting from doses such as were here administered even if continued for very long periods.

The hypocholesteremia of the stilbestrol-treated animals is also of interest. These very low cholesterol levels are difficult to reconcile with the essentially negative results obtained by administration of adrenotrophic hormone (Sayers *et al.*, 1944). Neither can they be ascribed to the poor nutritional state of the stilbestrol-treated animals for rats subjected to complete starvation for a similar period showed a significantly smaller serum cholesterol loss even though their body weight loss was far greater. It might be assumed, as an extension of the hypothesis of the Yale group, that the adrenal gland, subjected to continual and excessive stimulation by the hypersecreting hypophysis, is converting cholesterol at such an excessive rate that it exhausts its own stores as well as those of the serum. The tenability of such an explanation must, however, await further evidence.

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SUMMARY

The adrenal cholesterol of adult male rats fell to half the normal level as a result of exposure to barometric pressures of 200 to 300 mm. Hg. for periods of 1 to 7 hours. Animals dying during exposure, some after only 15 minutes, suffered a similar adrenal cholesterol loss. Those animals allowed to recuperate for 18 hours at normal atmospheric pressure showed complete restoration of the adrenal cholesterol stores. Exposure to low pressure had no effect on the serum cholesterol concentration.

Rats subjected to temperatures of 0 to 5° C. for 16 to 22 hours suffered a small loss of adrenal cholesterol but in those exposed to cold for 72 hours the cholesterol content of the adrenals was normal. Apparently exposure to cold causes an early depletion followed by later restoration of the adrenal cholesterol.

Complete starvation for 72 hours did not alter the cholesterol content of the adrenals although it did produce a slight but significant hypocholesteremia.

Prolonged treatment of unilaterally nephrectomized rats with large doses of desoxycorticosterone acetate caused irregular increases in the adrenal cholesterol content. The serum cholesterol concentration, however, was quite uniformly elevated.

Diethyl stilbestrol administration induced a rapid and progressive loss of cholesterol from the adrenal glands and from the serum. The resultant very low cholesterol levels were maintained for the duration of the longest experiment (34 days) without any indication of restorative changes. It is thought that stilbestrol produces this effect by stimulating the anterior hypophysis to secrete excessive amounts of adrenotrophic hormone and this substance, by causing adrenal hyperactivity, depletes the adrenal cholesterol content.

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NOTES AND COMMENTS

ESTROGEN-INACTIVATING LIVER EXTRACTS

It is well known that liver tissue "in vitro" inactivates estrone (Silberstein *et al.*, 1933; Zondek, 1934; Engel and Navratil, 1937; Heller, 1939 and 1940; Engel, 1941). It has been shown also that by implantation of ovaries into the mesentery (Golden and Sevringhaus, 1938), by implantation of pellets of estrogens into the spleen, or where they drain into the portal circulation (Biskind and Mark, 1939; Talbot, 1939; Glass *et al.*, 1940; Biskind, 1942; Biskind and Shelesnyak, 1942) and even by infrahepatic intravenous injection estrogens lose their characteristic biological effects.

It is very interesting that, in addition to these, synthetic estrogens such as diethylstilbestrol are inactivated by the liver (Zondek, Sulman and Sklow, 1943; Segaloff, 1944; Quintana, Lipschütz and Buzzone, 1944), although these substances are more resistant than estrone. This fact seems especially interesting because progesterone is quite resistant against inactivation by the liver (Zondek, 1941; Engel, 1944).

Most authors hold this inactivation to be due to enzymes (Zondek, 1934). Heller has shown that addition of sodium cyanide destroys the inactivating influence of the liver.

EXPERIMENTS

In our experiments we tried to extract the active principle from the liver. Zondek has shown that heating destroys the sterol-inactivating liver function. We used aqueous extracts of fresh beef liver at different pH's.

In a preliminary experiment we added to 100 grams of beef liver pulp 0.05 mgm. of diethylstilbestrol and kept them during eight hours at 37° C. An alcohol-acetone extract was made and tested in spayed, white mice, examining the vaginal smears after 48 to 100 hours. The diethylstilbestrol had lost 48 per cent of its estrogenic activity.

To another 100 grams of the same beef liver 0.5 mgm. of estrone were added and kept during eight hours at 37° C. We extracted in the same manner as indicated above and observed inactivation of 84 per cent.

Three aqueous extracts (No. 1, 2 and 3) were prepared from the same beef liver and later we repeated the experiment with three more extracts of another beef liver.

All these extracts were prepared by the following method: 100 grams of beef liver pulp were treated with 200 cc. of water at different pH's, as shown in table 1. The filtered extracts were neutralized. Then the estrogens were added to known quantities of the extracts and the mixtures kept for eight hours at 37° C. Afterwards we added five volumes of 96 per cent alcohol and filtered. The residue was washed with acetone; then alcohol as well as the

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acetone was eliminated and the residues gathered and suspended in sesame oil. These extracts were assayed by means of the Allen-Doisy test in spayed, white mice. Using boiled liver as a control, it was shown that practically the whole amount of estrogens can be recovered. Every experiment was carried out with estrone as well as with diethylstilbestrol.

In table 1 we are giving the results of these experiments with the corresponding pH of the aqueous solution, which played an important rôle. Zonedk *et al.* used in their experiments the same amount (0.02 mgm.) of estrone and of stilbestrol, whilst, taking in consideration that the estrogenic

TABLE 1

Extract number	pH	Extract quantity corresponds to gms. of beef liver	Estrone		Diethylstilbestrol	
			mgms.	loss in %	mgms.	loss in %
1	4	25	0, 1	84	0, 01	84
2	5.5	25	0, 1	84	0, 01	84
3	8	20	0, 1	0	0, 01	95
4	5	20	0, 1	90	0, 01	90
5	7	20	0, 1	84	0, 01	90
6	8.5	20	0, 1	0	0, 01	95

activity of estrone is much lower than of stilbestrol, we used ten times the quantity of estrone than of diethylstilbestrol, in order to have approximately the same biological activity of each of the two hormones. Besides that we took much higher quantities of liver than Zondek *et al.*

Our experiments having shown that the estrone inactivating factor of the liver is water soluble, we attempted to purify it as follows: 420 gm. of beef liver pulp were extracted with 420 cc. of water at pH 5, filtered and neutralized. Then five volumes of alcohol were added and the precipitate washed with acetone.

To half of the residue (extract No. 7) we added 0.1 mgm. of estrone. This mixture was kept for eight hours at 37°C. Afterwards we made an extract with alcohol and acetone in order to recover the estrogens and tested it in spayed, white mice. We found that 95% of the estrone was inactivated.

To the other half of the first residue 20 cc. of distilled water were added and this mixture was allowed to stand for 24 hours (extract No. 8). Then we filtered and precipitated with four volumes of alcohol. One tenth milligram of estrone was added to the precipitate and the mixture was kept for eight hours at 37° C. As a result, 80% of the estrogen was inactivated.

As extract No. 9 we used a concentrated commercial product, one gram of which corresponds to 100 gm. of fresh beef liver. To three grams of this product (equivalent to 300 gm. of liver) we added 0.1 mgm. of estrone and kept this mixture for eight hours at 37° C. We observed a loss of 84% of the estrogenic activity.

Repeating the last experiment with extract No. 9 we found the same result.

DISCUSSION

In the above mentioned experiments the inactivation of natural as well as synthetic estrogens by beef liver is shown.

Observations by Zondek, Sulman and Sklow were confirmed. Diverging

from these authors we did not use equal amounts of stilbestrol and estrone because of the different biological activity per milligram-unit.

The quantities of liver in our tests were higher than in those of Zondek *et al.* Whilst Zondek found stilbestrol more resistant against the inactivating liver factor than estrone (which corresponds to the clinical experience) we found the natural estrogens, at least in some cases, more resistant to aqueous extracts.

Acid extracts inactivate natural and synthetic estrogens in the same degree, but, whilst estrone withstands alkalin aqueous liver extracts, stilbestrol loses still more of its biological potency.

The anti-estrogenic factor is also to be found in concentrated liver extracts.

SUMMARY

Aqueous acid liver extracts inactivate "in vitro" estrone as well as stilbestrol. Alkalin extracts inactivate diethylstilbestrol, but fail to inactivate estrone. The active principle is to be found in extracts concentrated by alcohol precipitation.

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THE ADRENAL CORTEX AND THE LYMPHOCYTOPENIA OF STRESS[1]

It has been shown that with the injection of adrenal cortical extract, certain adrenal steroids, and adrenotropic hormone in the presence of the adrenal gland there is produced a reduction in the absolute count of lymphocytes (Dougherty and White, 1944). Adrenalectomy is followed by an

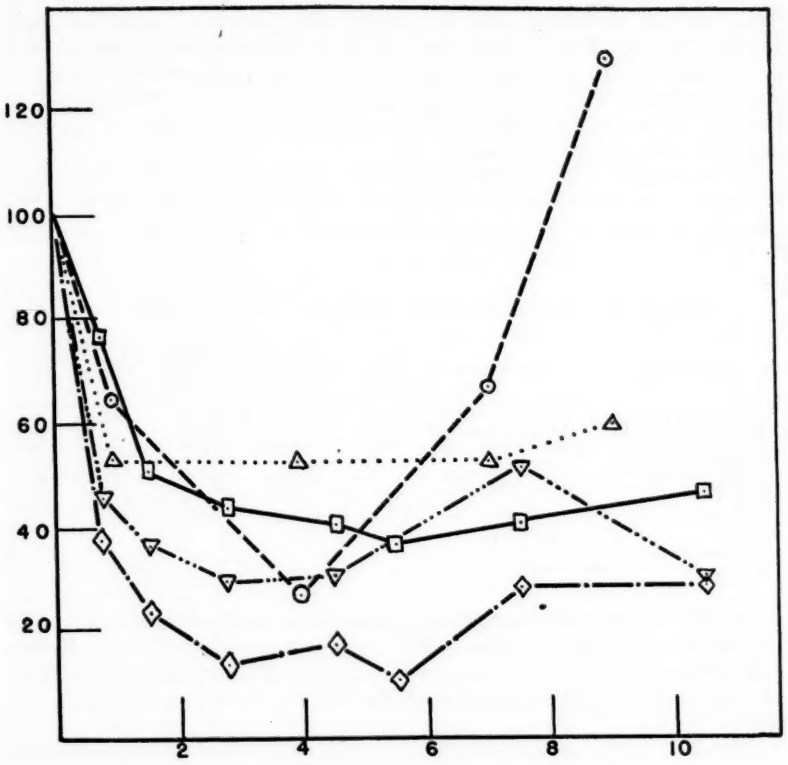

FIG. 1. The lymphocyte response of 5 normal male mice at various intervals, after being tied to a wire grid. The lymphoctye count at 0 times is taken as 100%. Abscissa: time in hours; ordinate: % change in lymphocyte number. Each symbol represents a single mouse.

increase in the lymphocyte count (Zwemer and Lyon, 1928; Corey and Britton, 1932; Waterman *et al.*, 1939), and there are reports that cerebral concussion (Van Valkenburg, 1933), acute infection (Piney, 1939), anoxia

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(Meyer Seever and Beatty, 1935) and generally the alarm reaction (Harlow and Selye, 1937) produce lymphocytopenia.

Experiments were conducted using normal, unilaterally and bilaterally adrenalectomized mice 40–60 days old. The operations were performed 18–24 hours before the application of the stress which consisted of tying the animal firmly to a wire grid, (Elmadjian and Pincus, 1944). Blood samples were obtained from the tail at intervals and the change in the absolute lymphocyte count was noted.

At about three hours after the initiation of the stress, the lymphocytopenia reaches its lowest point in normal mice and then there is a slight tendency to rise (Fig. 1). Only one animal, however, showed a return to its pre-stress level. In this case it rose above normal. This return to the pre-stress level and above normal might be explained by a possible adrenal exhaustion or some extra-adrenal lymphocytosis promoting effect as discussed by White and Dougherty (1945).

It was noted (Table 1) that unilaterally adrenalectomized animals under the same stress show a lag of about 45 minutes before the effect of the stress becomes apparent in the lymphocyte count and in 2 hours and 15 min. they do not show a drop as great as the normals.

TABLE 1. THE BLOOD LYMPHOCYTE RESPONSE TO STRESS IN TEST MICE

Type of stress	Type of animal	Number of animals	Mean pre-stress count	Mean count at 2.25 hrs. of experimentation	Mean lymphocyte count in stress as % of pre-stress value[1]
Tying to wire grid	Normal	11	12,540	4,696	40.0± 3.98
Tying to wire grid	Unilat. Adrenalect.	5	12,250	7,630	63.8± 4.56
Tying to wire grid	Bilat. Adrenalect.	5	15,600	12,452	90.5± 9.46
In refrigerator at 5° C.	Normal	2	15,450	8,200	53.0± 2.38
In refrigerator at 5° C.	Unilat. Adrenalect.	2	21,500	13,900	63.5± 4.16
In refrigerator at 5° C.	Bilat. Adrenalect.	2	16,900	17,950	105.5±14.86
None	Normal	8	9,777	10,906	110.5± 5.30

[1] Standard error $= \pm \sqrt{\frac{\Sigma d^2}{n(n-1)}}$.

The bilaterally adrenalectomized animals show no significant response to the grid stress and are prostrate and die soon after the stress. The small drop in the lymphocyte count of some of these bilaterally adrenalectomized animals may be due to changes in lymph flow (Cope, Brenizer and Polderman, 1942).

The data on the animals subjected to cold stress (Table 1) are presented for comparison with the more adequate trials of the grid stress. It can be seen that the same trends are exhibited, the unilateral adrenalectomized animals showing a quantitatively smaller drop than the normals, and those bilaterally adrenalectomized showing an insignificant rise.

Since statistically significant lymphocytopenia occurs under both types of stress in normal and unilaterally adrenalectomized mice and fails to occur in bilaterally adrenalectomized animals, it appears that some active adrenal hormone is responsible for the lymphocytopenia of stress.

Summary: A study is reported of the changes in lymphocyte count in 21 mice subjected to the stress of being tied to a wire grid, of 6 mice placed in a refrigerator at 5° C. and of 8 unstressed normal controls. In contrast to the relatively constant number of circulating lymphocytes in the unstressed con-

trols, there is reported a drop in lymphocyte number in the stressed unilaterally adrenalectomized and unoperated mice; stressed bilaterally adrenalectomized mice fail to show lymphocytopenia.

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NEW BOOKS

Antigens and Antibodies

FUNDAMENTALS OF IMMUNOLOGY. By William C. Boyd. ix+446 pp. Interscience Publishers, Inc., 1943.

THE SPECIFICITY OF SEROLOGICAL REACTIONS. By Karl Landsteiner. ix+310 pp. Harvard University Press. 1945. $5.00.

IMMUNO-CATALYSIS. By M. G. Sevag. ix+272 pp. Charles C Thomas. 1945. $4.50.

The initial phases of the science of immunology were concerned with the discovery and description of the phenomena which result from the reaction between antigens and their corresponding antibodies both *in vivo* and *in vitro*. The immunologist, however, has not remained satisfied with the mere observation of these reactions as biological phenomena; during the past few decades he has placed increasing emphasis on the discovery of their chemical basis, and on the measurement of the quantitative aspects of antigen-antibody reactions. There have been published many reviews and monographs dealing with these immunochemical problems. The three volumes presented in this review illustrate that, in a large measure, immunology can be considered today as a part of biochemistry.

As indicated by its title, Landsteiner's monograph deals primarily with the factors—analyzed as far as possible in terms of molecular structure—which determine the specificity of antigen-antibody reactions. The endocrinologist will also be particularly interested in a critical evaluation of the claims which have been made concerning the existence of anti-hormones(pp. 36–38). Sevag has attempted to show that all the known facts of immunochemistry can be described as the expression of enzyme-like phenomena, in which the antibody is the product of a reaction catalyzed by the antigen. Boyd's book can be more properly considered as the first text-book covering the field of theoretical and practical immunochemistry. It describes the chemical properties of antigens and antibodies; the methods for their quantitative determination; the kinectis of serologicalreactions; the application of immunochemistry to the fields of immunity, blood grouping, etc.

One of the chief problems of immunochemistry has been to define the properties which may permit a substance to act as an antigen, i.e., to elicit in the animal body a specific antibody response. It is now recognized that immunochemical specificity is conditioned not only by special determinant groups of the antigen molecule, but also by the total configuration of this molecule. Moreover, it is claimed by several authors—although denied by others—that certain complex antigens are able to elicit the production of multiple antibodies directed against their several determinant radicles. Much of the knowledge relating to immunochemical specificity has been derived from the analysis of the immunological behavior of synthetic antigens, the structures of which can be modified at will and correlated with modifications

in the antibody response. Understanding of the factors which determine the specificity of synthetic antigens has been applied to, and substantiated by, the study of the immunochemical behavior of a few natural antigens, for example of the polysaccharides elaborated by bacteria, erythrocytes and other tissues.

It has been possible in a few selected cases to describe the kinetics of antigen-antibody reactions in terms of the law of mass action, and to formulate reasonable hypotheses as to the type of chemical union which occur between the two components of the system. In fact, a chapter contributed by Pauling to Landsteiner's book offers some insight into the nature of the intermolecular forces (Van der Waal's attraction, hydrogen bond formation, interaction of electrically charged groups) which unite antigen and antibody. According to this author, specificity might be due to the fact that complementariness in structure of the two interacting molecules (antigen and antibody) permits non-specific intermolecular forces to come into fuller operation than would be possible for non-complementary structures.

There is almost universal agreement that antibodies are modified serum globulins, but the site and mechanism of production of the antibody, and the nature of the chemical difference between normal and immune globulins, remain highly controversial subjects. It has been proposed that, in the presence of the antigen, the normal synthetic processes are so modified that the globulin produced is—so to speak—molded on the antigenic molecule (lock and key relationship), thus giving rise to specific antibody. On the assumption that the fundamental polypeptide chains of normal and antibody globulin are the same, Pauling has postulated that the specific properties of the immune globulin are due to the fact that the antigen induces differences in folding of the polypeptide units. Sevag points out that, like inorganic catalysts and enzymes, antigens a) influence the formation of disproportionately large amounts of immune bodies, b) are not incorporated in the antibody molecule, c) only accelerate a reaction which is thermodynamically possible. On this basis, he comes to the conclusion that the antigen acts as a catalyst (enzyme) which modifies the normal globulin to produce the antibody. Antigen-antibody reaction would then correspond to the neutralization effect of the antibody (reaction product) on the antigen (enzyme). It is obvious that this type of parallelism between catalytic action and antibody production does not go beyond the level of formal analogy, and although interesting for speculation, cannot be considered as evidence of mechanism. We are greatly in need of more factual knowledge concerning the site of antibody production, and the chemical reactions involved in this process.

The theories outlined above do not account satisfactorily for the persistence of antibody long after both the antigen and the antibody initially synthesized have presumably been broken down. To overcome this objection, Burnet has suggested that the antigen modifies the intracellular proteases which are responsible for globulin synthesis. Under these conditions, the modified protease could retain the impress even after disappearance of the antigen; protein synthesis would return to normal only slowly as the cells grow and multiply, accounting for prolonged antibody production.[1]

Recent studies seem to establish that antibodies are first produced within the lymph nodes adjacent to a depot of antigen. It has been claimed further-

[1] Burnet, F. M.: The production of antibodies, 1941, Melbourne.

more that the lymphocytes themselves can store or produce both normal and antibody globulin.[2] Before reaching any final conclusion with regard to the type of cells involved in the synthesis of immune globulin, however, it will be necessary to take into account the special case presented by the production of antibodies against insoluble antigens, since lymphocytes are apparently unable to ingest particulate matter. It is worth considering that other types of cells may "prepare" the insoluble antigen for the lymphocytes; indeed there exists histological evidence suggesting that the cells of the reticulo endothelial system are involved in antibody production.[3]

[2] Conference on "lymph," to be published by Annals of the N. Y. Acad. of Sci., 1945.
[3] Sabin, F. R.: *J. Exp. Med.*, 1939, 70: 67.

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